Physiol Rev 94: 189–234, 2014
doi:10.1152/physrev.00036.2012

ENVIRONMENT AND BRAIN PLASTICITY: TOWARDS AN ENDOGENOUS PHARMACOTHERAPY

Alessandro Sale, Nicoletta Berardi, and Lamberto Maffei

Institute of Neuroscience, National Research Council, Pisa, Italy; Department of Psychology, Florence University, Florence, Italy; and Scuola Normale Superiore, Pisa, Italy

Sale A, Berardi N, Maffei L. Environment and Brain Plasticity: Towards an Endogenous Pharmacotherapy. *Physiol Rev* 94: 189–234, 2014; doi:10.1152/physrev.00036.2012.—Brain plasticity refers to the remarkable property of cerebral neurons to change their structure and function in response to experience, a fundamental theoretical theme in the field of basic research and a major focus for neural rehabilitation following brain disease. While much of the early work on this topic was based on deprivation approaches relying on sensory experience reduction procedures, major advances have been recently obtained using the conceptually opposite paradigm of environmental enrichment, whereby an enhanced stimulation is provided at multiple cognitive, sensory, social, and motor levels. In this survey, we aim to review past and recent work concerning the influence exerted by the environment on brain plasticity processes, with special emphasis on the underlying cellular and molecular mechanisms and starting from experimental work on animal models to move to highly relevant work performed in humans. We will initiate introducing the concept of brain plasticity and describing classic paradigmatic examples to illustrate how changes at the level of neuronal properties can ultimately affect and direct key perceptual and behavioral outputs. Then, we describe the remarkable effects elicited by early stressful conditions, maternal care, and preweaning enrichment on central nervous system development, with a separate section focusing on neurodevelopmental disorders. A specific section is dedicated to the striking ability of environmental enrichment and physical exercise to empower adult brain plasticity. Finally, we analyze in the last section the ever-increasing available knowledge on the effects elicited by enriched living conditions on physiological and pathological aging brain processes.

I. INTRODUCTION

The environment exerts profound effects on the brain. A large body of evidence shows that brain plasticity is strongly affected by exposure to stimulating environments, with beneficial consequences throughout the entire life span. We shall review the vast literature in this field outlining possible endogenous factors underlying the action of environment on brain plasticity.

This review is divided in six sections. In this first section, we introduce the concept of brain plasticity, presenting paradigmatic examples of experience-dependent neural plasticity and briefly outlining its general underlying mechanisms, to facilitate the discussion of environment action on plasticity factors later on in the review. We then introduce the concept of environmental enrichment and its nature, using classical examples from early studies and introducing the first documented effects on brain morphology and biochemistry. We then discuss the role of physical exercise as an essential component of environmental stimulation and the nature of enriched environment compared with naturalistic settings.

In the second section, we focus on the relationship between rearing conditions and brain development and plasticity, with particular attention to recent results obtained in the visual system model. We divide the survey of the literature in sections following the time course of development; wherever available, human data are included and discussed in parallel with the animal data. A specific section is devoted to the discussion of the literature on "enriching" the early environment in terms of tactile stimulation (massage) and on the effects of early environment in institutionalized children.

In the third section, we overview the effects of environment on brain plasticity in the adult. We survey both the litera-

ture on cognitive outcomes of the living environment and the more recent effects of environment on sensory system physiology. A section is devoted to discuss the effects of enriching the environment on adult visual cortical plasticity, prompted by recent results on recovery from amblyopia. Wherever available, human data are included and discussed in parallel with the animal data.

In the fourth section, we review the human and animal literature on the effects and mechanisms of action of environmental stimulation on brain aging, with particular attention to cognitive decline with age and to age-related neurodegenerative dementia.

In the last two sections, we summarize the main concepts emerging from the review of the literature on the action of the environment on brain function and plasticity, and we underline possible open questions and future research directions.

A. Concept of Brain Plasticity

The word *plasticity* conveys the meaning of pliability and malleability. Indeed, we can define brain plasticity as the capacity of neurons and of neural circuits in the brain to change, structurally and functionally, in response to experience. This property is fundamental for the adaptability of our behavior, for learning and memory processes, brain development, and brain repair.

Experience is translated in patterns of electrical activity within neural circuits, and it is the pattern of electrical activity which drives the different forms of functional and structural plasticity, through the spatially and temporally coordinated action of specific cellular and molecular factors. Neural plasticity may involve changes in the efficacy of already existing synaptic contacts, formation of new synaptic contacts or elimination of existing ones, large-scale changes in dendritic or axonal arborization, and production or signaling of neuromodulators or neurohormones.

B. Paradigmatic Examples of Brain Plasticity

Brain plasticity is evident both during development and in adult, and even in the aging brain. Basic molecular mechanisms of brain plasticity seem to be conserved across the lifetime; however, there are clear differences in the extent and magnitude of plastic changes between the developing and the adult brain, linked to the existence of critical periods, and there are examples of brain plasticity subserved by age-specific factors and processes (e.g., Refs. 160, 304).

1. Developmental brain plasticity

During development, genes and environment cooperate in building the brain, with experience guiding the final maturation of neural circuit and neural functions. Experience can shape neural circuit development because developing neural circuits are highly sensitive to experience, and they exhibit high neural plasticity, particularly during "sensitive" or critical periods of early development (50, 137, 197, 246, 279). Several classic examples of brain plasticity come from the study of processes governing development of sensory cortices. A common way to show the elevated plasticity of the developing brain and to investigate the underlying mechanisms has been to deprive a subject of experience in one sensory modality and to investigate what effects this has on sensory development. Visual cortex development has been the prime model to study experience-dependent plasticity and, since Wiesel and Hubel (526) first demonstrated that depriving one eye of vision in developing kittens (monocular deprivation, MD) caused dramatic changes in the proportion of cortical neurons driven by the deprived eye, MD has been one of the most exploited tools to probe cortical circuit plasticity. Many neurons in the visual cortex are binocular, i.e., receive input form both eyes, and exhibit different degrees of dominance from either eye, a property called ocular dominance (OD). MD, because of the alteration it causes in the pattern of electrical activity impinging onto visual cortical neurons, determines a massive shift in the OD distribution in favor of the nondeprived eye and a reduction of binocular neurons, accompanied by well evident structural changes, namely, small- and large-scale remodeling of synaptic connectivity on visual cortical neurons. Both functional and structural changes are driven by an activity triggered cascade of intracellular and extracellular factors (160, 202; see Refs. 198, 492 for review). At the level of visual perception, MD causes a strong reduction of visual acuity for the deprived eye and a loss of binocular vision (51). Thus, because of experience-dependent plasticity, the brain of a monocularly deprived animal is functionally and structurally different from the brain of a normal animal. This notion has been recently strengthened by the evidence that MD causes a specific increase in spine density in the visual cortex, and this increase persists even after normal binocular vision is restored, allowing complete functional recovery (207). This different brain is then differently affected, with respect to that of a normal animal, by a subsequent MD episode performed several weeks after the first (208): through structural plasticity, experience has left a trace which changes the way by which the brain responds to further experience.

OD plasticity has been shown to be maximal during a well-defined critical period and then to decline gradually, with different time courses in different species (see Ref. 50 for review). Its developmental time course is tightly controlled by cellular and molecular factors and in particular by development of intracortical inhibition (see Refs. 30, 37, 197, 279, 438, 492 for review) **(FIGURE 1)**. Different mechanisms between the juvenile and the mature visual system have also been documented at the level

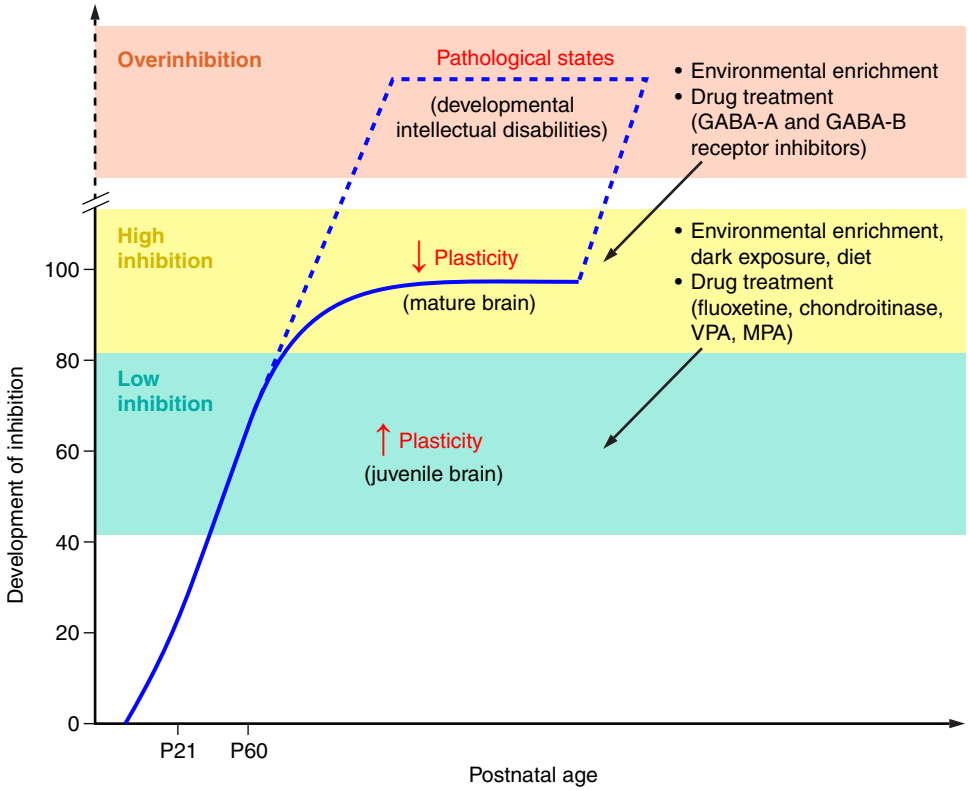

FIGURE 1. Developmental increase of brain GABAergic inhibition levels (normalized to the normal adult values; cyan curve) is paralleled by a progressive reduction of experience-dependent plasticity. Plasticity is high during early development (green block) and very low in the adult brain (yellow block). Anomalous increases in the strength of inhibitory neural circuits may lead to overinhibition linked to developmental intellectual disabilities (pink block), characterized by deficits in synaptic plasticity and neural development, like in Down's syndrome. Reducing GABAergic inhibition with either pharmacological or environmental treatments can increase plasticity in the adult brain, under both physiological and pathological conditions. VPA, valproic acid; MPA, mercaptopropionic acid.

of synaptic plasticity. While MD during the critical period first induces a long-term depression (LTD) of the deprived eye response, which is then followed by a delayed experience-dependent potentiation of the fellow eye, only the latter phenomenon does actually underlie OD plasticity in the adult (160).

Lack of experience in a sensory modality does not affect only the deprived sensory system: there is clear evidence for a crossmodal plasticity. As an example, the visual cortex of early blind, but not of sighted, subjects is activated during tasks of auditory localization, verbal memory, or Braille reading, in parallel with a better performance with respect to sighted subjects. If visual cortex activity is disturbed by trascranial magnetic stimulation (TMS) during these tasks, performance deteriorates in blind, but not in sighted subjects, showing that visual cortex activity is necessary for auditory localization, verbal memory, and Braille reading in the formers; this crossmodal plasticity underlies behavioral adaptation after sensory deprivation and relies on plastic changes in synaptic connectivity within and between cortical areas (see Refs. 38, 329). Again, different experience, different brains.

It has to be underlined that, in shaping the developing brain, experience continuously interacts with genetic information so that the final phenotype is the combined work of the individual genotype and the individual experience. As a consequence, much as lack of visual experience prevents visual cortical development, genetic mutations resulting in loss of function of proteins important for experience-dependent plasticity prevent visual experience from correctly guiding visual development (see, for instance, Ref. 51). The relation between gene and experience is, however, deeper than this. Genetic factors have been shown to interact with environmental factors, both at pre- and postnatal level, and it is the dynamic interaction between genes and environment which ultimately shapes the phenotype. As an example, which will be extensively dealt with in section II, exposure to early stress, such as peer rearing (rearing only with siblings in absence of the mother), produces an exaggerated response to stress later in life only in rhesus monkeys carriers of the short/long genotype for the serotonin transporter gene promoter, and not in animals with the long/long phenotype (81). It has to be noted that in animals reared with their mothers there is no difference between genotypes in response to stress (34). Therefore, neither the environment

(rearing condition) nor the genotype alters per se the response to stress: it is only the combination of genes and environment that brings about a different phenotype. A strong interest has been shown for the assessment of gene-environment interactions (G × E) in the development of disorders, such as development of antisocial behavior or depression in humans (see Ref. 81 for review).

2. Adult brain plasticity

Examples of neural plasticity in the adult brain are those underlying learning and memory processes or those following a deafferentation or lesion of cortical areas. When we learn a new motor or perceptual ability or form a spatial map of a new town which allows us to navigate within it or develop a fear response to a stimulus which occurs in connection with a harmful one, plastic changes of synaptic efficacy take place in neural structures belonging to the memory system specific for that form of learning and memory, such as, for instance, sensory cortices for perceptual learning, hippocampus for spatial memory, and amygdala for fear conditioning (320, 341, 471).

In fear conditioning, the temporal coincidence onto neurons in lateral amygdala (LA) of the arrival of sensory inputs relative to the initially emotionally neutral stimulus, the conditioned stimulus, and of inputs relative to the emotionally strong harmful stimulus, such as an electric shock, determine a long-term change in synaptic efficacy that enhances the response of LA neurons to the conditioned stimulus. This change is then able to trigger a fear response (see Ref. 224): the tone is no longer neutral; it evokes a negative feeling, a feeling of fear. The change elicited at neural circuit level and involved in the emotional response may remain for many days, as will the reaction of fear to the tone. Thus a specific experience has caused a plastic change in a specific neural circuit, and this is the reason why experience has modified the subject's behavior. While in the reported example a long-lasting potentiation of synaptic transmission is involved, that is a long-term potentiation (LTP) process, in other cases, experience causes a long-lasting decrease of synaptic efficacy, a LTD phenomenon. LTP and LTD are both thought to be critically involved in learning and memory processes (99, 320).

Fear conditioning offers the opportunity to observe another example of developmental change in brain plasticity: fear memories are more easily erased in young than in adult animals (238), and this might be linked to a change in the composition of extracellular matrix in the amygdala (176). Interestingly, the factors involved in the regulation of this critical period of emotional memory, the chondroitin sulfate proteoglycans, are the same factors contributing to the closure of OD critical period (393). This suggests that basic mechanisms of plasticity control are shared by different brain areas. Another consideration is important. While the acquisition of conditioned fear responses may have an adaptive role in promoting the safety of an individual, it may also underlie the acquisition of intrusive fear memories, as in the case of posttraumatic stress disorder (194). Fear conditioning is indeed largely exploited as a model to investigate the bases of emotional memory formation and regulation, and has been recently used to propose a new strategy to "rewrite" emotional memories, thus preventing the return of fear responses (451).

C. Maladaptive Plasticity

As well illustrated by the example of fear conditioning, neural plasticity is in itself neither good nor bad: it follows its rules toward structural and functional changes in connectivity, allowing experience to change our brain. If the outcome of the changes favors adaptive responses of the individual, we talk of adaptive plasticity. We have, however, examples of maladaptive plasticity, such as the development of a painful phantom limb after cortical deafferentation following limb amputation (150), which relies on mechanisms similar to those underlying cortical remapping after lesion, or the development of vulnerability to stress-related illnesses following cocaine assumption, which relies on epigenetic mechanisms (104). It is up to research to find the best ways to harness and guide neural plasticity towards adaptive and not maladaptive outcomes.

D. Mechanisms of Neural Plasticity

Synaptic plasticity is the major component of neural plasticity. The existence of synaptic plasticity in response to the pattern of electrical activity has been postulated by Canadian psychologist Donald Hebb, who thought it might underlie associative learning. He introduced the concept that the pattern of electrical activity is important to induce plastic changes in synaptic efficacy, and in particular the notion that the presence of a correlated activity between pre- and postsynaptic neurons promotes the potentiation of synaptic transmission; as a corollary, decorrelated activity promotes depression of synaptic transmission (472). In Hebb's statement, it is already present also the notion that synaptic plasticity involves both functional and structural changes. Homosynaptic LTP at excitatory synapses consists indeed of a prolonged increase in synaptic efficacy which involves both functional and structural modifications of synaptic contacts and is induced by repeated bouts of correlated pre- and postsynaptic activity. The temporal requirements for the pattern of pre- and postsynaptic activity has been now refined, since several studies have shown how synaptic efficacy can be increased (LTP) or decreased (LTD) according to the relative spike timing and firing rate of pre- and postsynaptic neurons (spike-timing-dependent plasticity) (55, 125, 181, 301, 310, 352, 461). Also, the level of previous activity in the circuit affects the probability that a given change of activity in the same circuit induces LTP rather than LTD (114).

Non-Hebbian forms of synaptic plasticity have also been observed: for instance, monocular neurons in the visual cortex responding exclusively to the deprived eye actually increase their responsiveness following MD (115, 343) as if they were trying to preserve their original drive. Therefore, in addition to plastic changes driven by synapse-specific electrical activity which follow hebbian rules, there seem to be forms of global feedback plasticity aimed at preserving neuronal total excitatory drive.

LTP and LTD have been observed in many brain areas, both cortical and subcortical (59, 306). The sequence of events leading to induction, expression, and consolidation of long-term changes of the LTP and LTD type has been recently reviewed (59, 99, 224, 286). The first step, the trigger for induction of LTP and LTD at glutamatergic synapses is, in most cases, dependent on the activation of glutamate *N*-methyl-D-aspartate receptors (NMDARs), which have classically been thought of as coincidence detectors of pre- and postsynaptic activity (215, 307). Activity of inhibitory inputs is also important for synaptic plasticity induction, since it will both regulate the pattern of activity in the circuit and the activation of NMDAR (see Ref. 197).

The opening of NMDARs during the induction of LTP leads to calcium entry that triggers a biochemical cascade involving intracellular kinases such as extracellular signal regulated kinase (ERK), cAMP-dependent protein kinase (PKA), calcium-calmodulin kinase type II (CaMKII), the end product of which are the first, rapid post- and presynaptic effects towards the expression of synaptic potentiation, which include potentiation of the 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid (AMPA) receptor-mediated excitatory postsynaptic currents (EPSC) (15, 224, 286, 306). The resulting Ca^{2+} transient determines the polarity of the induced plasticity, with low and prolonged Ca^{2+} transients inducing LTD and brief, steeper transients inducing LTP (see Ref. 59). A crucial step towards consolidation of long-term changes of synaptic efficacy is the synthesis of new proteins, either from existing mRNA (288) or following the activation of transcription factors such as the cAMP-responsive element-binding protein (CREB) by intracellular mechanisms mediated by kinase signaling (252, 276, 299). This allows local morphological modifications in synaptic contacts, for instance, at the level of dendritic spines, and provides consolidation of changes in synaptic efficacy. Neurotrophic factors such as the brain-derived neurotrophic factor (BDNF) are also strongly involved in expression and consolidation of synaptic plasticity (see Ref. 540 for review).

The presence of structural changes at synaptic sites has suggested the involvement of modifications of extracellular matrix (ECM) in synaptic plasticity. Indeed, ECM molecules regulate various aspects of synaptic plasticity (123, 394), and proteases acting on ECM molecules are involved in hippocampal LTP (25) and in visual cortex plasticity (197, 470).

It is important to underline that neuromodulators such as norepinephrine, acetylcholine, dopamine, or serotonin, which reflect the level of arousal, motivation, attention, affection, and emotion of a subject, are strongly involved in the induction and maintenance of synaptic plasticity (see Ref. 186 for a review). Striking examples from the visual system include the work by Bear and Singer (39) showing that OD plasticity in kittens is disrupted by pharmacological manipulations that simultaneously destruct cortical noradrenergic and cholinergic innervations, and by Dan studies (175) demonstrating that stimulation of the rat nucleus basalis decorrelates local cortical neuron responses via activation of muscarinic acetylcholine receptors, improving cortical representation of natural stimuli. An essential instructional role of the nucleus basalis has been also shown by Kilgard and Merzenich (237) for the reorganization of primary auditory cortex responses in the rat.

Finally, a crucial role in the consolidation of long-term neural plasticity is played by epigenetic mechanisms, including histone acetylation, which regulate gene expression (see Ref. 474 for review). For instance, mice with deficient histone acetylation activity exhibit induction but not maintenance of hippocampal LTP (8). Epigenetic processes are now thought of as mechanisms through which environmental dynamic experiences are inscribed on a fixed genotype, producing a stable alteration of the phenotype; as an example, which will be taken up again in section II, levels of maternal licking and grooming experienced by rat pups during the first days of life produce long-term effects on the feedback control of the HPA axis, an effect which involves the neuromodulator serotonin, thus programming anxiety-like behavior of pups once they become adult (see Ref. 328). In this case, the neural plastic event, i.e., memory of the experience, is due to epigenetic changes in the transcriptibility of the gene for the glucocorticoid receptors in hippocampal neurons, which modifies the response of the HPA axis to circulating glucocorticoids (518).

E. Adult Neurogenesis and Neural Plasticity

The presence of neurogenesis in the dentate gyrus (DG) of the adult hippocampus of mammals, humans included, demonstrated now almost 20 years ago (see Ref. 507 for review), has raised the question of its role in neural plasticity underlying learning and memory. Hippocampal adult neurogenesis is stimulated by voluntary running and by exposure to sensory, cognitive, motor, and socially enriched conditions (enriched environment), apparently by different means (see Refs. 229, 382, 507). The newly generated neurons in DG integrate with local circuits, receiving and establishing synaptic contacts, and are particularly susceptible to synaptic plasticity of the LTP type (5, 6, 446). Thus

hippocampal adult neurogenesis can be considered a form of activity-dependent brain plasticity, in which new neurons, and not just new synaptic connections, are added to neural circuits (229). The role of adult neurogenesis in hippocampus-dependent learning and memory is still under investigation (see Refs. 5, 6, 127, 434), and its relation with enriched environment will be dealt with in sections III and IV. The current proposal is that hippocampal neurogenesis might subserve specific aspects of memory formation and in particular that DG is responsible for separating memories that are formed in the hippocampus, for encoding temporal context, and for separating and differentiating between overlapping contextual representations (6, 7, 435, 436).

F. Concept of Enriched Environment

As introduced above, a quite direct approach to investigate the influence of experience on the brain is to manipulate the pattern of environmental stimulation to which animals are exposed. However, the possibility to quantify and measure environment-induced changes in the brain is relatively recent, dating back to the early 1960s, when the brain ceased to be considered as immutable and new experimental approaches were introduced to investigate the effects of experience on the brain. In parallel with the experiments performed by Hubel and Wiesel on the effects of MD on the anatomy and physiology of the visual cortex (525), fundamental contributions to the study of experience-dependent brain plasticity processes came from the introduction of the environmental enrichment (EE) paradigm by Rosenzweig and colleagues. These authors showed that exposure to EE dramatically affects brain morphology, chemistry, and physiology and elicits remarkable plastic responses ranging from molecular to anatomical and functional changes (for review, see Refs. 118, 424, 507).

Originally defined as "a combination of complex inanimate and social stimulation" (426), EE consists of wide and attractive cages where the animals are reared in large social groups and in the presence of a variety of stimulating objects that are regularly changed and substituted with others to stimulate explorative behavior, curiosity, and attentional processes. An essential component of the EE procedure is sustained voluntary physical exercise elicited by the presence of one or more running wheels. Thus EE definition is based on the comparison with alternative rearing conditions, such as the standard condition (SC), in which the animals are reared in small social groups and in very simple cages where only nesting material, food, and water are present, and the so-called impoverished condition (IC), in which social interactions are totally prevented because the animals are reared alone in individual cages, otherwise similar or even poorer than those used for SC. One of the most diffuse criticisms to the EE approach is that, since it may appear as a way of rearing the animals in a seminaturalistic setting more similar to the wildlife, its beneficial effects might not be real improvements in brain plasticity and function, but functional restorations to a physiological condition from deficits caused by the deprived setting imposed to laboratory animals. This critique has been present since the first studies on EE effects, and the first attempt to address it has been directed to assessing whether a laboratory-enriched setting could be considered a naturalistic environment. In a series of studies specifically aimed at addressing this issue (reviewed in Ref. 423), the Berkeley group found that laboratory rats living in a seminaturalistic outdoor setting for 1 mo had greater cortical development than their littermates reared in enriched laboratory cages, suggesting that even an enriched environment may still be relatively impoverished with respect to wildlife conditions, and that plasticity in response to stimulation does not reach saturation in a typical EE setting. The same conclusion was not true for ground squirrels, for which no differences were found in the weights of cerebral cortex between enriched and outdoor living animals. This species-specific effect underscores the need for further clarifications about the exact nature of the EE approach and does not allow to reach a definite conclusion. Reflections on the intrinsic nature of EE have continued throughout the years, and we would like here to present three arguments in favor of a specific action of EE, independently of its relationship with naturalistic outdoor conditions. First, as clearly stated by Mark Rosenzweig, the founder of the EE approach, it is unclear, for inbred laboratory animals, what exactly their natural environment can be, since laboratory rodents have been maintained for hundreds of generations in artificial enclosures, with a parallel genetic drift responsible for main differences in their gene pool with respect to the natural populations (423). Second, we recently underscored that, differently from a pure naturalistic condition, enriched animals are totally free to choose when and how much to experience the environmental richness, without contingencies and risks typically associated with living in the wild (437). Thus EE may provide the animals with a challenge-free space in which to train themselves in something more similar to a well-equipped gym or playroom. Third, as will hopefully become clearer in the following of this survey, increasing the quality and intensity of stimuli has remarkable beneficial effects also in humans, who typically do not experience impoverished living conditions. On the basis of these considerations, it is our opinion that the conclusion by which EE is just a way to reproduce more natural life conditions may not be appropriate.

Compared with other experimental paradigms based on a sensory deprivation approach (e.g., MD), EE appears as a rather mild treatment that gives one the opportunity to perform studies "for optimization" rather than "for alteration or reduction" of sensory experience. However, given the complexity and variability of the conditions adopted, concerns can be raised about a possible lack of standardization affecting EE experiments and their reproducibility.

This issue has been directly addressed in an elegant study in which distinct inbred strains of mice exhibiting well-known differences in behavioral tasks typically used in drug screening and behavioral phenotyping have been tested after a period of rearing in either SC or EE and in three different independent laboratories (533). EE was found to improve behavioral performances of each strain to the same extent in all laboratories, maintaining the expected behavioral differences between them, and in no case was the within-group variability of enriched animals increased with respect to the SC group. These results underscore the possibility to employ the EE protocol as a precise experimental treatment without the risk to obtain conflicting data in replicate studies, but the quoted study remains an isolated case of standardization attempt. Indeed, as will become clear in the following sections, differences concerning animal gender, age at EE onset, and EE duration and specific object setting are often evoked as a likely explanation for discrepancies and conflicting results; however, the possibility to use EE as a tool to investigate the impact of environment on brain health and plasticity is not jeopardized by these discrepancies, which only call for a more diffused practice of detailed description of EE protocols and standardization attempt.

The first studies on EE effects on the brain concentrated on anatomical, morphological, and biochemical effects (for review, see Refs. 118, 424, 507). Over the years, however, it has become clear that EE can exert powerful effects on neural plasticity, determining a conspicuous enhancement, for instance, of hippocampal synaptic plasticity and hippocampal-dependent learning and memory processes in adult animals (see Ref. 507 for review). It also emerged quite soon that EE affects almost all main factors involved in long-term synaptic plasticity, including NMDA receptors, inhibitory circuitry, intracellular kinases, transcription factors, neurotrophic factors, neuromodulators, epigenetic factors, and hippocampal neurogenesis (305, 309, 408, 409, 437, 507).

We will see in the following sections how extensive EE actions on brain plasticity are, and we will discuss the underlying mechanisms. We have dedicated section II to EE effects on brain development and developmental plasticity, section III to EE impact on adult brain plasticity, and the last section to the influence exerted by EE on the aging brain.

As will appear clear, most EE effects are common to those found in animals reared in standard cages where increased levels of physical exercise are possible thanks to the presence of a running wheel or a treadmill. Physical activity improves cognitive functions (84, 151, 256; for review, see Ref. 95), decreases HPA axis responsiveness (75, 358), attenuates motor deficits (243), increases angiogenesis (58, 218, 234), and enhances neurotrophin expression in the brain (140, 225, 244, 287, 312, 350, 362). Thus sustained physical exercise and EE can share common final pathways of cellular and molecular events, making it difficult to disentangle the relative contribution given by the exercise component present in the enrichment protocol, although early evidence has been provided that EE including enhanced motor activity is more effective than exercise alone in enhancing memory functions (53). However, more direct comparisons between running and enriched groups are needed to shed light on these processes, and to date, the principal outcomes of EE have not been clearly dissociated from an increase in voluntary motor behavior or exercise characterizing the enriched living condition (see Ref. 507).

II. ENVIRONMENT AND BRAIN DEVELOPMENT

In this section, we review the literature on the effects of environmental rearing conditions on brain development. We will start with a short survey of the impact of prenatal enrichment, to follow with a review of the influence exerted by exposure to EE in the preweaning period and by the impact of different amounts of maternal stimulation on brain development. Particular attention will be paid to recent results obtained in the visual system model. The section will end with two key examples of the profound impact that the environment can have not only on a physiological brain developmental course, but also when brain functioning is compromised due to the presence of genetic syndromes leading to developmental intellectual disabilities.

A. Prenatal Effects of Environment

During embryonic and fetal development, activation of orchestrated chains of genes is the prime driving force directing central nervous system maturational processes. Despite the overwhelming impact of this genetic control, the external stimuli have a strong influence on the developing structures, with the environment experienced by the mother exerting substantial effects on the intrauterine milieu, altering fetal organogenesis in a period of high susceptibility to external changes.

One obvious source of alteration is the maternal intake of food and pharmacologically active substances, or the development of illnesses and the exposure to environmental toxins and pollutants (476, 483). In addition to these strong and very direct modulators of fetal physiology, more subtle variations in the quality of environmental stimulation may also significantly affect the course of the ongoing developmental processes in the fetus. On the one hand, prenatal stress has a deleterious impact on fetal development (reviewed in Refs. 91, 174, 345). In humans, potential factors leading to prenatal stress include external sources impinging on the mother, such as exposure to major natural disasters, loss of the husband, divorce, serious illness or death of

a relative or friend, or internal sources, such as maternal disorders during pregnancy, anxiety, and depression. Thus the term *stress* is used here in its widest and most generic meaning, as every factor possibly leading to a strong and prolonged activation of the hypothalamic-pituitary-adrenal axis (HPA).

In humans, the severity of prenatal stress effects is likely dependent on a number of variables, including the proportion and persistence of the stressing agents and the individual maternal genotype and history that can affect resilience to stress (81, 433). This obviously introduces a strong factor of variability in epidemiological studies on the consequences of prenatal stress on the fetus; however, the literature consistently points to an increase in the risk of a number of adverse events under conditions of prenatal stress with respect to physiological pregnancies: among these events are fetal structural malformations leading to unexpected death, spontaneous abortion, preterm birth, and lower weight at birth (248), together with an increased probability to develop infantile spasms (454). These early effects are followed by long-term behavioral abnormalities (520), with retrospective studies relating prenatal maternal stress with several forms of severe psychopathology, including schizophrenia, depression, and anxiety (516, 536). Clinical evidence in humans is confirmed by a vast literature in animal models showing that stress during pregnancy is linked with growth retardation, morphological malformations, and alterations in motor development (46, 180), with significant behavioral deficits at adult ages, including anxious behaviors, social abnormalities, and impaired cognitive functions (164, 294, 398, 477).

The deleterious effects elicited by prenatal stress are thought to be strictly dependent on increased levels of circulating stress hormones in the fetus, produced by the mother under stressful conditions and crossing the placenta barrier (345). Even if some mechanisms exist that protect the fetus from maternal cortisol (especially in the human fetus), with the glucocorticoid metabolizing enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) acting in the placenta and in the fetal blood as a barrier for dangerous increments, the protective action of 11β-HSD2 may be bypassed, with an overload of glucocorticoids in the fetus escaping the inactivating mechanisms (536). Abnormal amounts of circulating stress hormones may eventually impact on key mediators of neural system development, like the neurotrophin BDNF, thus resulting in long-lasting alterations of synaptic plasticity (539).

On the opposite side of a continuum for the quality of environmental stimuli, EE during pregnancy may induce striking beneficial effects on human fetal development (400). In 2002, the American College of Obstetrics and Gynecologists recommended at least 30 min of moderate exercise during pregnancy on most days of the week as a way to promote benefits for the mother, fetus, and future newborn (2). In addition to well-recognized beneficial effects on amniotic fluid, placenta viability and body fat deposition (see, for instance, Refs. 97, 212), there is also an increasing number of studies documenting general neurodevelopmental benefits for the child deriving from maternal exercise during pregnancy. Among the available evidence, some exciting effects concerning increased Apgar scores and improved sensory and cognitive abilities in 5-yr-old children deserve particular attention (97, 190).

These effects in humans might be explained by data obtained in animal models: indeed, voluntary exercise in pregnant rats positively affects fetal growth (422), and the hippocampus of pups born from physically exercised mothers displays increased expression of BDNF and increased proliferation of progenitor cells in the granule layer (56, 374). Moreover, high levels of maternal physical exercise during pregnancy have long-lasting effects on the offspring, enhancing their cognitive abilities at very early and older postnatal ages (274, 374) and providing protection from neurodegeneration in old age (200). Similar effects have been also found in the offspring of rats exposed to EE during pregnancy, which in addition display, when they reach adult ages (250), signs of increased synaptic elaboration and complexity in the hippocampus, such as higher expression of the neural cell adhesion molecule (NCAM) and of the major synaptic protein synaptophysin (3). A strong impact of maternal enrichment on fetal development has been also documented by our group in the visual system, with prenatally enriched fetuses displaying faster dynamics of neural progenitor migration and spontaneous apoptosis in the retinal ganglion cell layer, an effect mediated by the insulin-like growth factor I (IGF-I) (440). We proposed a model in which sustained physical exercise during pregnancy increases IGF-I in enriched mothers, promoting an increased placental transfer of nutrients to the fetus; this would in turn lead to larger amounts of IGF-I autonomously produced by the fetus (153), resulting in the accelerated development detectable at the retinal level.

B. Influence of Maternal Care and Preweaning Environmental Enrichment on Brain Development

1. Influence of maternal care

Experiences acquired between birth and weaning are essential in promoting and regulating the neural development and the behavioral traits of the newborn in rodents and primates (149). During this critical period of high developmental plasticity, maternal influence can be considered one of the most important sources of sensory experience for the developing subject (206, 289, 421), regulating physical growth and promoting neural maturation of brain structures involved in cognitive functions (149). This issue has

been intensively studied in laboratory rodents, in which maternal behavior consists of stereotyped modules that can be easily investigated and manipulated in controlled experimental conditions.

One of the best-characterized effects of maternal influence is the development of stress responses exhibited by the offspring when they become adult (for authoritative reviews, see Refs. 147, 156). The neuroendocrine response to stressors strictly depends on the activity of the HPA axis, which is under the inhibitory control of the hippocampus. Under stressful conditions, two neuronal populations located in the paraventricular nucleus of the hypothalamus and in the central nucleus of the amygdala liberate the corticotropin-releasing factor (CRF), which in turn acts on adrenal glands eliciting the release of glucocorticoids, key mediators of the organism response to stress. A brief (3–15 min) period of daily maternal separation in rat and mouse pups (a treatment called "handling") during the first two postnatal weeks decreases the magnitude of stress response in adulthood at both the behavioral and endocrine level (reviewed in Ref. 327), while longer periods (3–6 h) of daily separation from the mother (a treatment usually called "maternal separation") elicit the opposite effect, enhancing the responses to stressor agents (262, 505). Moreover, maternal separation has also been associated with increased susceptibility to disease and adult cognitive deficits (205, 361, 402), while handled animals show, as adults, improved immune system function and a greater amplitude of LTP in the hippocampus (467, 529). A strong relationship between early nurturance and stress modulation has also been reported in nonhuman primates (141, 372).

The detrimental effects of maternal separation are thought to be a direct consequence of the long-lasting perturbation of the delicate relationship between the mother and the newborn, resulting in a reduction in the levels of maternal care experienced and in a remarkable stress for the developing pups, which display increasing glucocorticoid levels during the separation period, and suppressing cell responses to growth hormone, prolactin, and insulin, three major trophic hormones (257). Even if the reaction displayed by separated pups can appear as a complex unified process, behavioral and hormonal changes do not act as a whole in response to the absence of the mother, but rather consist in a number of distinct modules under the control of specific thermal, tactile, and nutritional stimuli associated with the dam, which have been called "hidden regulators" of the infant physiology (204). Among them, maternal licking and grooming behaviors directly regulate pup somatic growth through maintenance of appropriate levels of specific hormones, as exemplified by the reduced activity of ornithine decarboxylase (494) in separated pups. Ornithine decarboxylase is an enzyme that catalyzes the decarboxylation of ornithine, a product of the urea cycle, to form putrescine, a critical step in the synthesis of polyamines, which are in turn essential for stabilizing DNA structure. Interestingly, the detrimental effects of maternal separation are prevented by artificial procedures of pup stimulation resembling maternal licking behavior (377).

While the mechanisms involved in the effects of maternal separation are well characterized, the beneficial outcome of handling raised a debate concerning the nature of the regulatory processes involved (see Ref. 156). It has been proposed by Seymour Levine that changes in mother-pup interactions are at the core of the effects elicited by postnatal handling; in particular, it has been proposed that handled pups receive increased levels of maternal care with respect to undisturbed animals (for review, see Ref. 113). This hypothesis turned out to be correct, as directly demonstrated by Meaney and collaborators, which showed that mothers of handled pups display enhanced levels of licking/grooming and arched back nursing, an active and particularly efficacious feeding posture (289). This explains a point which might seem counterintuitive; that is why a brief separation from the mother elicits beneficial effects on pups: handled pups receive higher levels of maternal care. Further support to the idea that the main effects elicited by early postnatal handling are mediated by maternal behavior alterations stems from those studies comparing the behavior of adult animals that experienced different levels of maternal care during their first weeks of life. In the rat, there are large variations in maternal care levels naturally displayed by dams, making it possible to isolate subpopulations of mothers exhibiting high or low maternal engagement (for details, see Ref. 87). It has been repeatedly demonstrated that the offspring of the most proficient mothers show reduced fearfulness and stress levels as adults, compared with those displayed by offspring born and cared by less attentive dams. Thus the offspring of mothers characterized by high care levels resemble, as adults, those subjected to handling during the first days of postnatal life (74, 290). The long-lasting consequences elicited by elevated amounts of maternal stimulation extend beyond physiological processes linked to stress responses, enhancing learning and memory abilities, promoting structural synaptic plasticity and increasing hippocampal BDNF (289, 464, 504). Perhaps the most elegant proof of a causal relationship between maternal behavior and emotional and cognitive development in the offspring are the results of cross-fostering studies showing that the adult phenotype of a litter is strictly dependent on the amount of care provided by the adoptive mother, not by the biological one (156, 289).

Parental separation in the form of isolate-rearing or peer-rearing or alterations in the amount of parental care received during development due to early parental loss, neglect, or abuse exert a dramatic influence also in non-human primates, modulating adult vulnerability to stress-related psychopathology and leading to long-lasting impaired cognition (373).

Another important behavioral trait under maternal behavior control is the maternal style exhibited by adult females, which typically resembles that of their care givers, both in rodents and in primates (148, 300). In rodents, neural centers, like the medial preoptic area (MPOA) and the ventromedial nucleus of the hypotalamus, which are involved in the control of maternal behavior expression (357), are particularly sensitive to the influence of maternal care experienced during the first week of life. It has been proposed that early life experience through maternal care stimulation can be the basis for a nongenomic characterization and transmission of individual differences in stress reactivity, cognitive functions, and maternal style across generations (148).

Which are the biological bases for this powerful control driven by early experiences on brain and behavior? Considerable advances have been done concerning knowledge of the molecular mechanisms involved in the environmental programming of individual differences elicited by maternal behavior. Meaney and co-workers (518) have shown that differences in HPA response to stress displayed in adulthood by the offspring of highly or less active caring mothers depend on different amount of DNA methylation in the promoter of the glucocorticoid receptor (GR) gene in the hippocampus. DNA methylation at the level of cytosine residues (415) is a stable epigenetic mark in postmitotic cells strongly affecting levels of gene transcription, with hypomethylation being usually associated with active chromatin structure and transcriptional activity (235, 414). Another crucial epigenetic mark is acetylation of NH_2-terminal tails of chromatin histones, which is a direct regulator of chromatin structure and function and which undertakes a bilateral relationship with DNA methylation (107). Although DNA methylation has been traditionally viewed as almost impermeable to postnatal environmental influences, Weaver et al. (518) showed that the hippocampus of the offspring raised by the most active mothers undergoes, during the first postnatal week of life, a process of demethylation at the level of the GR promoter, specifically inside the binding sequence for the NGFI-A transcription factor (518). This difference in DNA methylation is long-lasting, rendering the sequence of GR gene promoter more accessible to transcription-factor binding and thus resulting in increased GR gene expression; this explains the typical phenotype of reduced stress response exhibited by rats that have experienced intensive maternal care levels during infancy, since the efficiency of the feedback control on the production of stress hormones is enhanced by the higher number of hippocampal GRs. DNA methylation levels in the brain can be also dramatically affected by maternal nutrient intake during pregnancy (reviewed in Ref. 321), not only in rodents but, strikingly, also in primates (497).

The discovery of an epigenetic regulation of GR gene expression has opened exciting possibilities of artificial manipulation of the neuroendrocrine response to stress in subjects exposed to early adversities. It has been shown that the methylation state of the GR gene promoter can be reversed in adulthood by injecting Trichostatin A (TSA), a compound inhibiting the mammalian histone deacetylase (HDAC) family of enzymes, leading to increased histone acethylation levels, into the brain (518). TSA treatment of pups which received low levels of maternal care during the first postnatal days of life results in increased acetylation, reduced methylation, and enhanced expression of the GR gene, with a full normalization of the HPA response to stress. On the contrary, intraventricular injections of methionine, which is converted by methionine adenosyltransferase into the methyl donor *S*-adenosylmethionine (SAM), which is in turn known to stimulate methylation (321, 375), increases stress responsiveness and promotes anxious behaviors in the adult offspring of the most proficiently caring mothers (519).

Overall, these results demonstrate that early environmental experiences can profoundly affect the adult phenotype through epigenomic processes impinging on the structure and function of chromatin (328, 517). Epigenetic changes seem also involved in the enduring consequences of maternal care on maternal style exhibited by the offspring. Increased maternal care levels are associated with a higher expression of the estrogen receptor alpha in the MPOA, due to lower levels of cytosine methylation in the receptor gene promoter (88).

In humans, vast epidemiological evidence suggests that early alterations in maternal care have durable or even permanent effects on the individual personality traits, cognitive abilities, and vulnerability to disease (228), with a specific role for early life maltreatment in the etiology of stress-related disturbances (163). Much of the available knowledge derives from the study of children who were abandoned at birth and placed in orphanages, and in particular studies conducted in Bucharest orphanages, showing that orphans reared in harsh conditions characterized by very little attention from caregivers often suffer from a kind of "institutionalization syndrome" which comprises several growth delays and neurobiological/behavioral alterations, including a low intelligence quotient (IQ), disorganized forms of attachment, impaired language abilities, and a tendency toward a pathological social-emotional development (543). Importantly, enhanced caregiving through placement in therapeutic foster care can strongly alleviate these symptoms (154, 351), possibly acting on brain circuits involved in the control and regulation of emotional responses, such as the amygdala (490). This is in agreement with data obtained in animal models showing that EE from the time of weaning can reverse the effects of maternal separation on stress reactivity (155). By tracking the cognitive development of institutionalized children randomly assigned to continued institutional care or to placement in foster care, Nelson et al. (351) highlighted the existence of a sensitive

period for cognitive function maturation. Indeed, the authors found that children placed in foster care in early periods (0–18 and 18–24 mo) displayed better performance than those placed later on (24–30 and above 30 mo) (351). Very little evidence is present in noninstitutionalized children trying to compare the effects of different levels of maternal care. Recently, a study has provided compelling evidence for a direct link between the quality of early nurturance and brain development, showing that maternal nurturance objectively assessed during the preschool period is predictive of larger hippocampal volumes at school age (296).

The "orphanage" effect is strongly reminiscent of Harry Harlow's results obtained in maternally separated rhesus monkeys (420, 458). Total social deprivation of primate infants usually results in extremely severe and permanent abnormalities, with a typical range of motor stereotypies and aggressive and anomalous parenting behaviors (193). Milder forms of maternal deprivation, such as the so-called peer-rearing obtained by maternal separation at birth followed by a short period of hand-rearing and then long-term rearing inside large groups of same age peers, do not usually result in anomalous physical and motor development, but tend to produce neophobia, social demotivation, and behavioral impulsivity (475).

The advent of the "behavioral epigenetics" era (278) has opened exciting possibilities to investigate the biological mechanisms underlying long-lasting neural effects of early life adversity not only in rodents, but also in humans. Childhood abuse is known to alter HPA stress responses and to increase the risk of suicide. Focusing on a neuron-specific glucocorticoid receptor (NR3C1) promoter, a recent study showed increased cytosine methylation and decreased glucocorticoid receptor mRNA in the hippocampus of suicide individuals with a history of childhood abuse (322), providing a link with the previously documented epigenetic effects of parental care in the rat. This is further supported by analysis of whole-genome methylation patterns in children raised since birth in institutional care, showing greater methylation levels, compared with children raised by their biological parents, in genes involved in the control of immune response and cellular signaling systems (349).

2. Influence of preweaning EE

Despite the large amount of data concerning the effects of maternal stimulation on neural development, the possibility that early exposure to EE might modulate the maturation of brain circuitries has remained scarcely investigated for many years.

The limited interest attracted by early EE studies can be possibly attributed to the fact that preweaning EE involves little amounts of voluntary physical exercise, as pups are too inert to engage in sustained motor activities. Since increased levels of physical activity are thought to be an essential component of the enrichment protocol, this can explain why the possibility to evoke neural and behavioral changes through preweaning EE has been considered quite limited. For instance, differently from adult animals, hippocampal neurogenesis was not found to be promoted by an intensive preweaning EE protocol consisting of increasing complex combinations of tactile, olfactory, visual, acoustic, and vestibular stimuli to which pups were exposed from postnatal day 7 (P7) until P21 (249). However, since early EE provides increased levels of polysensory stimulation occurring during a period of high anatomical and functional rearrangement of the cerebral cortex, it might be expected to elicit brain changes through experience-dependent plasticity processes. Accordingly, more complex dendritic branching has been found in cortical pyramidal cells following EE occurring in the P10-P24 period, particularly in the parieto-occipital cortex (510). A significant increase in neuronal cytodifferentiation has been also found in the motor cortex of rats submitted to EE from P5 to weaning, with enriched subjects showing better performance in a number of behavioral adaptive responses, as measured in the open field, narrow path crossing, hindlimb support, and ascending on a rope (376). Koo et al. (250) showed that granular cell layer neurogenesis and hippocampal and cortical expression levels of NCAM, synaptophysin, and BDNF are significantly increased in the cerebral cortex of preweaning enriched subjects compared with standard reared pups; interestingly, all these molecules are involved in synaptic plasticity processes. It is also worth noting that prenatal stress and early EE may interact with each other. Postnatal EE has been demonstrated to reverse disturbances induced by prenatal stress in social play behavior and in the ability to respond to restraint stress (340), and to counteract defects in cognitive ability, cell proliferation, and synaptic protein expression in prenatally stressed rats (250, 272).

In 2004, we started at the Institute of Neuroscience of the National Research Council (CNR) in Pisa a new endeavor in which we combined the rigorous methodological approach followed in classic visual system studies with the conceptual frame of EE. This approach has proven quite fruitful, allowing us to probe the impact of environmental stimulation on brain developmental plasticity (437). Focusing on the progressive increase of visual acuity that occurs during early postnatal life in most mammals, we showed that the time course of this highly sensitive parameter of visual system development is robustly accelerated in mice and rats exposed to EE since birth (76, 268), leading to higher visual acuity values even in adulthood (76), a result in agreement with previous work by Prusky et al. (401). In the time scale of human visual development, it can be estimated that this effect corresponds to an acceleration of ~2 years in the 5-year time-lapse usually required for a child to reach adultlike visual acuity. A remarkable acceleration of visual system development was also evident when taking

into account the possibility to evoke long-lasting changes in layer II–III synaptic transmission of visual cortical slices (240), with an earlier time course for LTP inducibility occurring in enriched pups compared with standard-reared animals (76). Searching for possible molecular factors underlying the effects of EE, we found an early increase of BDNF protein content in the visual cortex of P7 enriched pups, together with an enhanced expression of the GABA biosynthetic enzymes, GAD65 and -67, detectable at the same age and also 1 wk later (76). It is interesting to observe that exactly the same functional and molecular changes have been previously found by our group, in collaboration with Susumu Tonegawa at MIT, in mice engineered to overexpress BDNF in their forebrain (214). In these animals, large BDNF increments obtained from very early postnatal ages lead to a faster maturation of intracortical GABAergic inhibition, directly causing earlier developmental increases in inhibitory postsynaptic currents and GAD65 levels in the perisomatic region of pyramidal cells, together with an accelerated maturation of visual acuity and closure of the sensitive period for LTP in visual cortical slices. Thus one first conclusion of our study was the possibility to reduce the effects of an early enriched experience to those elicited by a neurotrophin crucially involved in visual system development.

Another major achievement we obtained was the demonstration that, in addition to BDNF, IGF-I has a key role in driving the acceleration of visual development under EE conditions. IGF-I expression, indeed, turned out to be increased in the visual cortex of preweaning enriched rats, and IGF-I supply or blockade was respectively able to mimic or prevent the EE effects on visual acuity maturation (96). Given that an increased GAD65 expression, a feature usually associated with enhanced BDNF signaling, was also present in visual cortex synaptic terminals of IGF-I-infused rats, it is possible that, as previously shown in the adult rat by the group of Torres-Alemann (78) and demonstrated in the developing retina (see below), an increase in brain IGF-I in the EE setting stimulates the expression of BDNF in the visual cortex. Eventually, activation of BDNF and IGF-I signaling may regulate the nuclear activation of key target genes: CREB/CRE-mediated gene expression is developmentally accelerated in enriched animals, and chronic injections of standard-reared pups with rolipram, a pharmacological compound increasing the phosphorylation of CREB, mimic the effects of EE on visual acuity maturation (76).

While a classic and intuitive view predicts that maturation of neural circuitries in specific sensory systems is dependent on inputs of the same sensory modality, the precociousness of the effects we obtained in enriched animals challenged this dogma, offering an attractive example of visual system acceleration following molecular changes occurring at ages that precede eye opening (P15) and even photoreceptor formation (P7). This observation opened the way for two different lines of further investigation. On the one hand, we showed that enriched rats raised in complete darkness during development, a treatment usually associated with a severe delay in the maturation of visual cortical circuits (e.g., Refs. 138, 486), had a visual acuity maturational process equal to that displayed by standard-reared animals raised in normal light (36). A full compensation for the detrimental effects induced by dark-rearing is also evident in BDNF overexpressing mice (172), confirming the critical role for this neurotrophin, even in the absence of visual experience, in driving visual system maturation.

On the other hand, we looked for possible cues in the EE setting that might be responsible for the earliest effects occurring in enriched pups. An obvious hypothesis was that maternal behavior differences were present between enriched and nonenriched dams, leading to different amounts of sensory stimulation provided to the litters. A detailed quantitative study of maternal care in different environmental conditions confirmed this hypothesis (444), showing that enriched pups experience constant physical contact due to the presence of adult females in the nest and receive much higher levels of maternal and nonmaternal licking and grooming, fundamental sources of sensory stimulation at early ages (444). The critical role of tactile stimulation for visual system development was further demonstrated in a study in which we reproduced the EE-dependent acceleration of visual development and increase of brain IGF-I levels by providing standard-reared rat pups, during their first 10 postnatal days of life, with a cycle of artificial massages mimicking maternal behavior (188). Thus living in an EE setting provides the animals with an additional source of stimulation other than the social, cognitive, and motor components: maternal touch.

In parallel with the effects obtained in rats, we also reported that enriching the environment by practicing "massage therapy" in healthy preterm infants (gestational age between 30 and 33 wk), results in increased levels of plasma IGF-I, faster developmental reduction in the latency of flash visual evoked potentials (VEPs), and an increase in behavioral visual acuity, which persisted above 2 mo after the end of the treatment (188). Moreover, massaged babies displayed faster EEG maturation, as evident from a more rapid shortening of the interbust intervals, a reliable index of the developmental stage of the brain. In addition, while preterm control infants exhibited changes in EEG spectral power in the first postnatal weeks, these changes were prevented in preterm massaged infants; as a consequence, the maturation of brain electrical in the latter group was more similar to that observed in utero in term infants (189). These results add to the previously published literature concerning the beneficial effects of infant massage on weight gain and adaptive behavior (448, 512), to show that early EE interventions may also dramatically affect brain development in humans.

The social environment we recreated with our EE paradigm in rodents included more litters raised together by several dams sharing their care-giving, a form of early social stimulation usually referred to as "communal nesting," which is typical of the natural reproductive behavior of many rodent species. It has been shown that adult mice that have been raised in communal nesting display higher propensity to interact socially, reduced anhedonia during social stress, and reduced anxiety-like behavior when placed in a novel environment, together with higher nerve growth factor (NGF) and BDNF levels in brain areas such as the hippocampus and the hypothalamus, accompanied by lower corticosterone levels after exposure to social stressors (65, 66, 106). Moreover, this effect is transgenerational, with communally reared females displaying enhanced maternal care and reduced anxiety-like behavior as adults (106). It is important to underscore that, beside the effects set in motion by communal nesting, licking was also enhanced in a more selective EE setting where no social contribution to maternal care was possible because only one dam was reared with her litter in the absence of any other adult female (444). Since the increment in maternal care was linked with enriched mothers spending a significantly longer time out of the nest, one can speculate that raising pups from birth in an enriched environment when only one dam is present may represent a particular form of "handling-like effect," because the higher amount of time spent by the mother out of the nest in the enriched cage leads to increased amounts of licking (444).

Surprisingly, not only the development of the visual cortex, but even that of retina, a structure traditionally considered little or not plastic at all (27, 138, 144), shows a marked acceleration under EE conditions, as evident when taking into account both retinal acuity development and the process of retinal ganglion cell dendrite segregation into ON and OFF sublaminae (266, 268). An interplay between BDNF and IGF-I is involved also in this case, suggesting that it might be a general feature of the EE impact on visual plasticity (266–268). The responsivity of the retina to environmental stimulation in rodents is further supported by the alterations of anatomical and physiological maturation of retinal circuits caused by a complete lack of visual experience in mice (484, 485).

The positive impact of early EE is not restricted to the visual system. Rats housed in enriched conditions prior to reaching sexual maturity show a variety of effects in the primary auditory cortex: increased strength of auditory responses, increased number of sound-activated neurons, better sensitivity to quiet sounds, better selectivity for tone frequencies and enhanced directional selectivity of auditory cortical neurons (129, 544). Moreover, EE from birth accelerates the maturation of chondroitin sulfate proteoglycans (CSPGs) in the striatum, resulting in better performance in behavioral tasks requiring mixed cognitive and motor competences at P10 (459). Finally, exposure to EE from birth accelerates the maturation of GABAergic and glutamatergic synapses in the mouse hippocampus, with a faster transition from excitatory to inhibitory GABA action (196), and promotes the morphological development of dentate granule cells (291).

It should be noted that while the effect of CNS accelerated maturation induced by early exposure to EE offers a strong proof of concept for the remarkable influence of the environment on the dynamic building of the brain, it should not be viewed as necessarily beneficial in all contests. Speeding up the maturation of a developing circuit, indeed, might force the maturational process within excessively narrow critical periods, reducing the interaction with environmental stimuli required for a proper development or cause a temporal mismatch with the maturation of other developing circuits. This seems not the case for the visual and auditory system development, where no adverse consequences of early enrichment have been reported so far, or for cognitive and emotional development, which are rescued by EE from the negative effects of prenatal stress. However, the possible negative consequences of overstimulation should not be neglected, particularly during development. In addition to activation of stress responses, excessive stimulation in one or two domains might result in deficient stimulation in other domains, with negative consequences for development. The EE protocols employed in laboratory practice do not result in excessive stimulation, since no activity is imposed or forced upon the animals; moreover, the effects of environmental stimulation in very young animals are mediated by maternal behavior, and both enhanced maternal care levels and massage reduce circulating corticosteroids, and therefore do not result in a stressful overstimulation.

These considerations lead us to ask ourselves which aspects of the EE paradigm in rodents might actually be applicable to children. Except for the aforementioned results obtained in massaged babies, very little is known of the effects elicited by enriched living conditions in children. Previous studies showed that early educational and health enrichment at ages 3–5 yr is associated with long-term increases in psychophysiological orienting and arousal at age 11 (407) and that an enrichment program including early nutritional, educational, and physical exercise stimulation resulted in lower scores for schizotypal personality, antisocial behavior, and criminal behavior at age 17–23 yr (406). Despite the scarcity of the available information, these results encourage further research focused on the long-lasting effects of early EE on the brain. The available results in animal models would suggest that key elements of an enriched environment would be the opportunity, for each individual, to be voluntarily engaged in cognitive, including perceptual, and motor activities of interest, the presence of novelty elements eliciting curiosity and exploration and, particu-

larly for very young subjects, the presence of adequate social interactions and physical contact.

C. Rescuing Developmental Intellectual Disabilities

Given the multifactorial action of EE on brain plasticity, this paradigm could have a favorable impact on a host of neurological disorders characterized by alterations in neuronal plasticity processes occuring during development. One particularly relevant case is that of the so-called developmental intellectual disabilities, a heterogeneous group of disorders characterized by cognitive impairment and affecting 2–3% of the population in the industrialized world (for a recent review, see Ref. 142). As an example of EE potentiality in the field, here we focus on Rett syndrome, a very severe disorder which offers one of the most striking examples of pleiotropy in humans, and on Down syndrome, the most diffused genetic cause of mental retardation.

Rett syndrome is a progressive disorder that predominantly affects the female population in early childhood. After a period of apparently normal development, developmental stasis and rapid deterioration occur at 6–18 mo of age, resulting in a complex neurological and neurobehavioral phenotype with mental retardation and severe dysfunctions in motor coordination skills (191). This deterioration is caused by loss-of-function mutations in the *X*-linked gene encoding the methyl-CpG binding protein (MeCP2) (10), a key regulator of gene expression and RNA splicing (85, 542), with a particularly relevant action on BDNF (94). Down syndrome is caused by triplication of chromosome 21 (Chr21) (275).

Interestingly, it has been proposed that both syndromes may have a common key etiologic mechanism consisting of a general dysregulation of the cerebral balance between excitatory and inhibitory drive, leading to impaired synaptic plasticity in several brain structures (142) **(FIGURE 1)**. This view is mainly based on studies performed in transgenic murine models of these pathologies. Indeed, detailed electrophysiological analysis in mice carrying conditional deletion of MeCP2 or neuron-specific expression of mutated protein forms shows cortical and hippocampal reductions in cell activity (21, 109) and reduced LTP expression in various brain regions (21, 337), an effect generally attributed to overinhibition. Recently, it has been elegantly demonstrated that MeCP2 knockout mice display a progressive shift in cortical excitation/inhibition balance favoring inhibition, through early upregulation in the expression of parvalbumin GABAergic neurons synapsing onto cortical pyramidal neurons (128). In Ts65Dn mice, the prime model of Down syndrome (110), a large number of studies have shown that the cognitive impairment is mainly related to overinhibition in temporal lobe circuitries (43, 242, 383, 456), with a central role of excessive inhibition being confirmed by the demonstration that administration of GABA-A and GABA-B receptor antagonists reverses the main deficits in this model (143, 241) **(FIGURE 1)**. In agreement with these data, analyses of human postmortem brain samples have shown increased density of GABA receptors in people with Rett syndrome (60) and an impaired balance between excitatory and inhibitory systems in Down syndrome tissues (see Ref. 419 for a recent review).

In the absence of a definite and safe pharmacological treatment for these disorders, manipulating the environment as a way to modify the brain biochemical milieu and to favor functional recovery may emerge as an alternative and attractive way of intervention. Preweaning EE stimulates BDNF expression in the brain, leads to a partial rescue of motor and cognitive abilities, and reverses cortical LTP deficits in mouse models of Rett syndrome, increasing the number of cortical excitatory synapses without any changes in the density of inhibitory synapses (293). During typical development, inhibitory cortical interneurons follow their developmental trajectory under the influence of BDNF, which progressively increases during development (214). In developmental disorders, inhibitory interneurons might derail from the typical developmental trajectory and show an enhanced action even in the presence of lower levels of BDNF. EE might partially rescue the phenotype not acting on the runaway intracortical inhibition, but on intracortical excitatory circuitry.

Martinez-Cue and co-workers (314, 315) reported beneficial effects elicited by EE in Ts65Dn mice, an effect that turned out to be gender-specific, and Dierssen et al. (121) showed a more complex branching in the dendritic trees of Ts65Dn mice. Moreover, EE combined with increased levels of physical exercise increases neurogenesis and gliogenesis in the hippocampus of Ts65Dn mice of both genders (86). Beneficial effects on learning abilities have been also associated with increased levels of physical exercise, with exercised 10- to 12-mo-old Ts65Dn male mice displaying improved performance in the Morris water maze task and an increase in hippocampal neurogenesis, as suggested by a higher number of doublecortin (DCX) positive neurons (292). We recently tested the therapeutic potential of EE in the Ts65Dn model by focusing on both hippocampal and cortical functions. Our findings show that EE promotes recovery from cognitive impairment and synaptic plasticity failure and induces a full rescue of visual acuity, ocular dominance, and visual neuronal response latencies in Ts65Dn mice compared with their littermates reared in standard conditions, an effect accompanied by normalization of GABA release in both hippocampal and visual cortex synaptosomes (42).

In view of possible interventions in human developmental disorders, data for Rett animal models suggest that the earlier the intervention, the better the outcome (293); for

Down syndrome, it is also conceivable that early interventions should be preferable to maximize the chance to positively impact on brain developmental processes altered by the trisomic condition. The nature of the intervention should have the characteristic outlined before, that is, novelty and opportunity to be voluntarily engaged in cognitive and motor activities of interest; in case of very early interventions, a component of physical contact such as massage might be envisaged.

In conclusion, there is robust evidence that the prenatal, preweaning, and postweaning environment shapes brain development. Physiological brain development is enhanced in enriched subjects, and EE can prevent or rescue deficits associated with pathological brain development. Factors that emerge as crucial mediators of EE effects on brain development are IGF-I, BDNF, inhibition/excitation balance, and epigenetic processes, which might be responsible for the long duration of some EE effects.

III. EFFECTS OF ENVIRONMENT ON BRAIN PLASTICITY IN THE ADULT

A. Environmental Stimulation and Brain Morphology

Initial experiments by Rosenzweig et al. (427) showed that after 30 days of exposure to enriched living conditions, the cortex of adult rats increased robustly in thickness and weight compared with that of standard reared animals. These changes occurred in the entire dorsal cortex, including frontal, parietal, and occipital cortex, but were more prominent in the visual and hippocampal area (409, 424, 514, 515), leading to the widely accepted notion that some specific brain regions are more sensitive to experience-dependent activation compared with others. Since then, many studies performed in different species from rodents to primates have reported various anatomical changes associated with enriched living conditions, including nearly all structural components analyzed, such as an increment in the size of the soma and of the nucleus of nerve cells, increased dendritic arborization, length of dendritic spines, synaptic size, and number, as well as increased postsynaptic thickening, gliogenesis, and brain vascularization (18, 58, 119, 120, 173, 184, 185, 210, 253, 336, 493, 494). The social component characteristic of EE, albeit not sufficient to account for all documented beneficial effects (426), can act in an additive manner with the other sources of stimuli, as suggested by early studies reporting that synaptic density, number of synapses per neuron, and maximum length of synaptic contact zone are highest in enriched rats, intermediate in socially reared rats, and lowest in isolates (460, 493). Moreover, rearing rats in isolation leads to characteristic neuroanatomical changes, including smaller brains, larger lateral ventricles, and reductions in cortical and hippocampal volume (111, 136, 452).

Another striking effect elicited by EE during adulthood is an increase of hippocampal neurogenesis. Although in mammals the majority of neurons are generated by the time of birth (83), the dentate gyrus of hippocampus maintains this potentiality after sexual maturity, not only in rodents (187, 258), but also in monkeys (177) and, remarkably, even in humans (132); of note, a very recent paper estimated that humans have at least as much adult hippocampal neurogenesis as mice, with one-third of adult hippocampal neurons turning over (468). Numerous studies pioneered by Fred Gage and co-workers have shown that exposure to an enriched environment produces a significant increase in hippocampal neurogenesis (68, 230–233), an effect caused also by enhanced levels of physical exercise through running (68, 508). The two treatments, albeit similar, seem to act with distinct mechanisms: while voluntary exercise alone in a standard cage increases neurogenesis with an increment in both proliferation of neuronal precursors and survival of new-generated neurons, exposure to an enriched environment mostly affects the number of surviving newborn cells (135, 508). On the contrary, environmental impoverishment through social isolation reduces hippocampal cell proliferation, survival, and neuronal differentiation in mice, rats, and prairie voles (216, 285, 295, 522). The ability of EE to interact with the programs of nerve cell renewal extends over the influence on neurogenesis, including also the capability to reduce apoptotic cell death in the rat hippocampus under both natural and insulting conditions (541).

These results challenge the traditional vision that the anatomical structure of the adult brain is immutable under nonpathological conditions, revealing an unexpected plasticity at the structural level. Similar effects can occur also in the human brain: learning to juggle and practicing it for 3 mo lead to a transient and selective expansion in grey matter in the midtemporal area and in the left posterior intraparietal sulcus, which are regions involved in the processing and storage of complex visual motion (124).

B. Environmental Stimulation and Molecular Changes

Efforts aimed at understanding possible molecular mechanisms underlying the reported changes elicited by different environmental conditions on the brain are guided by the intent to reveal factors that are susceptible to be manipulated to reproduce the beneficial effects of the enriched experience. First studies by Rosenzweig and co-workers (425, 428) reported an increase in acetylcholinesterase activity, with subsequent investigations confirming and extending this initial observation to the other neurotransmitter systems which have diffuse projections to the entire brain, like the serotonin (32, 67, 412) and norepinephrine systems (133, 347), with opposite effects induced by protocols of social deprivation (57, 165, 313, 344), although the effec-

tive outcome of this form of impoverishment can be gender-dependent (see Ref. 325). Since these neuromodulators have been reported to influence learning and plasticity in the adult brain (186, 507) while, at the same time, they are also tightly involved in the regulation of brain arousal (54, 203), these studies opened at the time a debate which contrasted the so-called "learning and memory hypothesis" of EE with the "arousal hypothesis" (see Ref. 507). In our opinion, these two hypotheses are not necessarily mutually exclusive, and there is no necessity to contrast one with the other; indeed, arousal has a component of global attention which favors perception and learning and memory processes, in this latter case also facilitating the synaptic plasticity mechanisms underlying memory formation and consolidation, as previously discussed. Therefore, an effect of EE on arousal can be seen as a component of EE positive effects on learning and memory. Another possible effect that EE could exert on learning and memory via an action on neuromodulatory systems is an effect on sleep states. To date, very few studies have characterized the impact of EE on sleeping states (334); given the importance of sleep for memory consolidation (410), these aspects and the underlying molecular mechanisms need further investigation.

One group of molecules particularly sensitive to environmental stimuli and exerting potent functions in the nervous system are the neurotrophic factors (or neurotrophins), a class of secreted proteins promoting neuronal development and survival, which include not only the already mentioned NGF and BDNF, but also neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4). Neurotrophic factors are strongly implicated in regulating structural and functional neural rearrangements in response to sensory stimulation, both during development and in the adult brain (reviewed in Refs. 49, 62, 481), thanks to their capacity to act as ideal players following the classic Hebb's principle of activity-dependent plasticity of the nervous system. One of the best-characterized effects of EE is to stimulate brain expression of various neurotrophic factors (reviewed in Ref. 390), resulting in higher levels of mRNAs for NT-3 and NGF in the visual cortex and hippocampus (488, 489) and increasing protein levels of NGF, BDNF, and NT-3 in several brain regions (76, 217, 390, 443). In addition, EE increases hippocampal phosphorylation of CREB (541), which is known to regulate BDNF expression (479). Sustained levels of physical exercise occurring either in EE or as an individual component of environmental stimulation can increase brain uptake of other physiologically relevant trophic factors, such as IGF-I, which mediates most of the known effects of exercise on the brain, including increased expression of BDNF and c-*fos*, an indicator of neuronal activity, increased hippocampal neurogenesis, and protective effects against brain insults (78, 79, 251, 491). Recently, EE has been also linked with chromatin modifications through increased histone-tail acetylation (146).

New possibilities for investigating brain molecular changes elicited by environmental stimulation came from the development of gene chip analyses, allowing simultaneous screening and comparison of differential gene activation in different environmental conditions. It has been reported that exposure to an enriched environment even only for 3 h elicits robust long-lasting changes, with most of the affected genes being grouped in functional classes linked to neuronal structure, synaptic plasticity and transmission, neuronal excitability, neuroprotection, and learning and memory capacity (236, 408). Another powerful tool of investigation has been provided by the advent of conditional gene knockout techniques. Genetic deletion of the NMDA receptor for glutamate in the CA1 subregion of the hippocampus has been associated with profound learning deficits, largely or completely rescued after 2 mo of EE (409). On the other hand, overexpression of the NR2B subunit of NMDA receptors in the forebrain enhances learning and memory abilities with a ceiling effect, occluding further improvements after exposure to an enriched environment (478). This saturation suggests the existence of overlapping mechanisms between EE and genetic enhancement of the NMDA receptor functions, offering an informative example of interplay between nature and nurture whereby a genetic deletion can be compensated through environmental stimulation, while occlusion of the influence of environment is achieved through genetic enhancement of learning and memory functions.

C. Environmental Stimulation, Synaptic Plasticity, and Behavioral Changes

As EE selectively promotes structural elaborations especially evident in the cortex and hippocampus, a general rule can be also found at the behavioral level, with EE enhancing animal performance mostly in tasks involving superior cognitive functions, such as learning and memory. Since the initial anecdotic observations dating back to Donald Hebb, these effects have been replicated in a great variety of different studies under controlled experimental conditions. One of the most robust effects on the behavior of laboratory rodents appears in hippocampus-dependent tasks involving spatial memory, such as the Morris water maze task, where the animals learn to reach a submerged platform relying on a spatial map based on the position of visual stimuli external to the pool (reviewed in Ref. 108). EE enhances spatial learning and memory in the Morris water maze, independently on the gender and age of tested animals (e.g., Refs. 139, 259, 342, 364, 378, 480, 527). Some uncertainness exists about cellular mechanisms underlying the improvement in behavioral performances elicited by EE in special memory tasks, but an increase in hippocampal LTP, a universally accepted model of cellular memory and activity-dependent modification of synaptic efficacy (298), has been shown in animals after living in complex environmental settings, together with increased synaptic transmission and

synaptic strength (20, 126, 152, 183, 308, 506). More specifically, a recent analysis of possible underlying causes for enhanced LTP at Schaffer collateral inputs in enriched animals revealed an increase in the frequency but not in the amplitude of miniature excitatory postsynaptic currents, with no effect on presynaptic release probability (309). Furthermore, EE increased neuronal excitability by reducing spiking threshold, leading CA1 pyramidal neurons to fire more action potentials in response to excitatory postsynaptic potentials. Finally, a striking effect of EE on hippocampal dendritic plasticity has been documented, with compartmentalized increases of excitability in specific dendritic branches of CA1 pyramidal neurons, due to changes in the distribution of dendritic spike propagation mediated by decreases in the activity of Ca^{2+}-sensitive voltage-gated K^+ channels (305).

The effects induced by EE on learning and memory are not limited to spatial abilities, as shown, for instance, in the systematic behavioral analysis performed by Rampon et al. (409), in which the enriched experience was reported to enhance mnemonic performances in mice in three different nonspatial tasks, one of which universally acknowledged to be hippocampus independent (i.e., cued fear-conditioning task).

Taking into account the general impact of environmental stimulation on the behavior, a special interest is given to those studies investigating the influence of EE on emotionality and stress reaction, a very important theme given the well-documented relationships of stress levels with cognitive function (219, 297, 445). While the issue about a possible capacity of enriched experience to lower stress levels has remained controversial for long time, the prevailing consensus is that enriched animals display less behavioral anxiety and stress (90, 269, 431), together with significant reductions in basal corticosterone levels (44), although this effect can be abolished in particular conditions in which more males are group-housed and social disturbances might occur (324, 325). Furthermore, it has been shown that EE can abolish the elevation of glucocorticoids elicited by a mild repeated immune challenge (335) or by stressing protocols based on a mild electric shock, with enriched animals displaying higher natural cell killer cytotoxicity, an effect not abolished by the stressing procedures (45). These studies show that pathways of communication between the immune and the nervous systems are subjected to environmental influence, with important implications for the growing field of psychoneuroimmunology.

A very recent study suggests that the programming of the energy balance and food intake system is also affected by EE, with the interesting possibility of the existence of a sensitive period; indeed, only mice enriched from birth, but not mice exposed to EE when adult, show decreased leptin, despite similar adipose mass, but normal food intake. This effect is based on an enhanced leptin signaling and higher excitatory input on anorexigenic neurons in the arcuate nucleus of the hypothalamus found in young EE mice (303). This is the first evidence that early experiences can affect one of the most primary behaviors in an individual, that is, feeding behavior.

D. Effects of EE in the Adult on Sensory Systems and Discrimination Abilities

Exposure to enriched living conditions has been shown to profoundly affect the functional properties of mature sensory systems.

Transferring rats to a naturalistic environment, promoting the execution of the complete, natural behavioral repertoire of this species, induces a large-scale functional and morphological refinement of cortical somatosensory maps in the barrel cortex, causing a contraction of the whisker cortical representation, associated with smaller receptive field size (397). Morevoer, exposure to EE induces marked changes in the synaptic circuitry of layer IV of the somatosensory cortex, promoting an increase in the number of synapses (264), and EE has also been associated with increased somatosensory-evoked potentials (116). These findings are supported by behavioral studies reporting faster learning of tactile discrimination of textures in adult rats exposed to an enriched environment compared with rats reared in impoverished conditions, in which a degradation of forepaw representation in somatosensory cortex has been demonstrated (63, 102).

In the posterior auditory field, EE has been recently associated with increased spectral and temporal selectivity and time-locking to rapid input sequences (222), in agreement with previous studies showing improvements in response strength, threshold, selectivity, and latency of primary auditory cortex neurons, together with their directional selectivity (129, 544). These changes are able to affect behavioral spatial localization in the auditory system, with enriched animals displaying improved sound-azimuth discrimination performance (73).

In the visual cortex of enriched cats, a higher proportion of orientation-selective cells and sharper orientation tuning has been reported compared with impoverished controls, together with higher contrast sensitivity and spatial frequency resolution (40, 41). Moreover, an increased paired-pulse depression of the visual thalamo-cortical pathway has been described in enriched rats, which may suggest a higher neurotransmitter release probability by thalamic afferents (302).

While one obvious source for the effects of EE on sensory cortices is the specific input belonging to the same sensory modality, a functional crosstalk between different

cortical areas may also be involved. One intriguing possibility is that the primary motor cortex, whose activation is likely to be enhanced under enriched conditions due to increased levels of physical exercise, may in turn activate other brain areas, thus providing a means for a more widespread diffusion of the enrichment effects. Neill and Stryker (354), for instance, have provided compelling evidence that running increases the firing rate of V1 neurons. Since, however, no recording of cell activity from the motor cortex has been performed in this study, it remains unknown whether visual cortical neurons are actually directly affected via activation of the motor cortex or whether running acts through a modification of the animal behavioral state, for instance affecting attention levels. Simultaneous recordings of local field potentials in awake animals, indeed, showed that EE actually results in reduced coupling levels between the electrical activities of motor and visual cortical areas (117).

E. Empowering Brain Plasticity in the Adult: Lessons From the Visual System

In the last few years, a series of provocative studies have provided tremendous challenges to the dogma of a rigid critical period strictly regulating visual cortex plasticity early in life in mammals with a binocular vision **(FIGURE 2)**.

One paradigmatic field that is undergoing fast and paramount changes in its conceptual and methodological framework is that of amblyopia therapy in the adult (31). Amblyopia (lazy eye) is a severe condition with an estimated prevalence of 1–5% in the total world population (211) and constitutes the most common cause of monocular visual loss in children (411, 449). Amblyopia is caused by a functional imbalance between the two eyes occurring early in development, a defect that, if not rapidly corrected through proper visual penalization strategies of the fellow eye, results in a dramatic degradation of visual acuity and contrast sensitivity in the anisometropic, strabismic, or cataract-affected eye, with a number of other perceptual deficits, including stereopsis defects (211, 239, 535). In animal models, amblyopia is induced by long-term occlusion of vision through one eye by means of an enduring MD procedure starting at the peak of plasticity during the critical period and protracted until subjects reach adulthood.

Using a rat model of amblyopia, we showed that adult amblyopic rats transferred to an EE setting for 3 wk immediately after being subjected to reverse suture (i.e., reopening of the long-term deprived eye and closure of the eyelids in the fellow eye) undergo a full recovery of their visual functions, both in terms of visual acuity and binocular vision (29, 443). Beneficial effects on visual discrimination abilities were detectable at both the electrophysiological and behavioral level, and outlasted the end of the treatment for at least 10 days. Recovery of plasticity in enriched animals was accompanied by increased expression of BDNF, decreased density of CSPG perineuronal nets, and a threefold reduction in GABA release detected in the visual cortex contralateral to the previously amblyopic eye by means of in vivo brain microdialysis, without any significant change in the release of glutamate. The reduction in the intracortical inhibition-excitation balance elicited by EE was causally linked with the functional rescue of visual functions, as definitely demonstrated by the complete lack of visual acuity and ocular dominance recovery in enriched rats intracortically infused in their visual cortex with the benzodiazepine Diazepam (443). This has been one of the first demonstrations that reducing GABAergic inhibition promotes adult visual cortical plasticity, in agreement with Takao Hensch's work on the fundamental role of inhibition as a crucial regulator for the critical period in V1 (reviewed in Refs. 197, 198, 338, 438) (**FIGURES 1 AND 2**). In agreement with this hypothesis, a reduction of intracortical GABAergic inhibition by infusion of a blocker of GABA synthesis (3-mercaptopropionic acid, MPA) or of a GABA-A receptor antagonist (picrotoxin) in V1 reinstates juvenile-like plasticity in the adult visual cortex (192).

It is interesting to point out that while, during development, an increase in BDNF levels elicited by EE promotes the maturation of the GABAergic system in the visual cortex, in adult animals enhanced BDNF is associated with reduced GABA release in the EE setting. We have proposed that distinct processes link these molecular factors together in different periods of the animal life (30). Specifically, while it is well established that an early increase in BDNF is a prime trigger for the maturation of inhibitory circuitry in the immature brain (214), on the contrary, the increased expression of BDNF in adult animals may be one of the consequences of a reduced inhibition/excitation balance, which can increase the expression of various genes involved in neural plasticity.

More recently, we went on to address the possibility to rescue visual acuity in long-term deprived adult rats exposed to EE immediately after silencing of retino-thalamic projections of the fellow (nonamblyopic) eye due to optic nerve dissection (487). This represents a case of particularly relevant clinical interest, since a significant number of amblyopic patients lose their better eye due to accidents or ocular illnesses, thus becoming severely visually impaired (511, 530). No spontaneous recovery of visual abilities was detected in animals reared under standard environmental conditions, but a full rescue of visual acuity was achieved in monocular rats exposed to EE, accompanied by lower numbers of GAD67-positive cells and increased BDNF expression in the visual cortex (487).

Given its totally noninvasive nature, EE appears as a promising strategy to counteract visual impairments in human

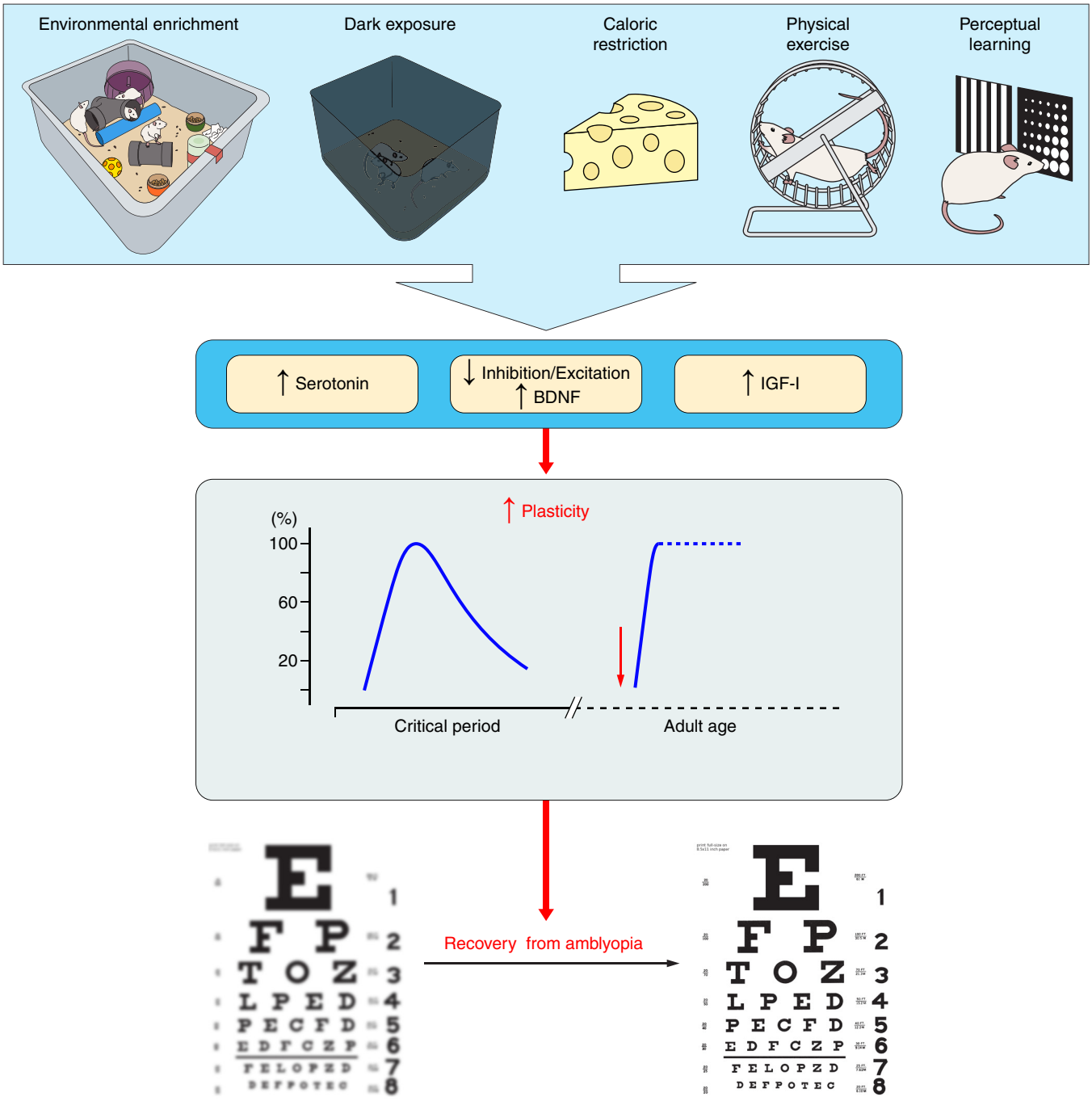

FIGURE 2. Environmental strategies restoring plasticity in the adult visual system. Recent data have documented a previously unsuspected high potential of neuronal plasticity in the adult visual cortex. This can be elicited by various noninvasive strategies, such as living in an EE setting, dark exposure, caloric restriction, attaining high levels of voluntary physical exercise, and being engaged in visual perceptual learning training. Enhancement of cortical plasticity is achieved through modulation of critical underlying molecular factors, including enhanced release of the neurotransmitter serotonin, reduced inhibition/excitation balance, and increased expression of trophic factors such as BDNF and IGF-I. The enhancement of neural plasticity achieved by these treatments (red arrow) is exemplified in the figure by reopening of a sensitive phase for plasticity in the adult brain, well after the closure of the critical period in V1. The blue curve on the *left* depicts the developmental time course of visual cortical plasticity, expressed as a percentage of the maximal plasticity levels at the peak of the critical period; the blue curve on the *right* depicts the increase in adult visual cortical plasticity following onset of one of these treatments. At the functional level, this may eventually lead to visual function recovery from amblyopia in adult animals.

amblyopia. One step up toward the application of the EE paradigm to clinics is investigating the role of independent EE components (e.g., social, sensory, motor) in reproducing the beneficial effects elicited by the entire enriched experience, and then designing therapeutic approaches based on the most promising and effective variables. Recently, we evaluated the efficacy of motor activity, social stimulation, and enhanced visual stimuli in promoting amblyopia recovery in the rat model (28). The results showed a full recovery of ocular dominance and visual acuity both in animals experiencing high levels of voluntary motor activity in a running wheel and in rats exposed to a protocol of visual enrichment consisting in a rotating visual drum. A strong involvement of visual experience in the recovery process is suggested by the results obtained with amblyopic animals maintained under classic EE conditions in a completely dark room, which did not display any sign of visual function recovery. This is not at odds with previous results by the group of Quinlan and co-workers (195), showing that a period of dark exposure before the animals were reverse-sutured and reexposed to normal light conditions promotes vision recovery in adult amblyopic rats **(FIGURE 2)**; in our paradigm, indeed, the animals were reverse-sutured and immediately transferred to darkness in an EE setting, therefore lacking a period of reverse-suture experience in the light.

In contrast to motor and visual enrichment, social stimulation alone did not favor restoration of normal visual acuity and ocular dominance. The EE components effective in triggering recovery from amblyopia were associated with decreased GABA release in synaptosome analysis, without any change in the release of glutamate, thus resulting in a decreased intracortical inhibition/excitation ratio (28).

These findings might encourage the implementation of new environmental strategies devoted to promote stimulation of the amblyopic eye in adult patients as a way to increase their chance to undergo significant visual functional improvements. Accordingly, a growing body of evidence in humans shows that experimental paradigms analogous to EE, such as playing video games or being trained in visual perceptual learning (PL) tasks, can be quite successful in eliciting amblyopia recovery in adult subjects (22, 182, 281, 282). In search for possible cellular and molecular mechanisms underlying PL effects, we set up a model of visual PL in rodents (441). We first trained a group of animals to practice in distinguishing between two vertical gratings differing only for their spatial frequency; then, we made the spatial frequencies of the two stimuli progressively more similar to each other, until the animal performance fell to chance level. A daily discrimination threshold was measured, revealing a progressive improvement of discrimination performance with training. Control animals were required to only discriminate between an unchanging grating and a homogeneous gray panel (a purely associative task), matching the overall swim time and number of training days with those of PL rats. Activation of V1 circuitries in trained animals was confirmed by the strong selectivity of the PL process for grating orientation. Within 1 h from the last discrimination trial, LTP from layer II–III of V1 slices appeared occluded in PL animals compared with controls, both when testing its inducibility in vertical connections (stimulating electrode placed in layer IV) and when stimulating at the level of horizontal connections (stimulating electrode placed in layer II/III). Moreover, a significant leftward shift toward increased amplitudes of field excitatory postsynaptic potentials was found in the input/output curves of trained animals compared with controls (441). Thus these data fulfill two of the most commonly accepted criteria used to relate LTP with learning, i.e., occlusion and mimicry, indicating that visual discrimination improvements in PL rats can be explained in terms of long-term increments of synaptic efficacy in V1. This is consistent with the critical role for LTP in mediating learning in other brain areas such as the amygdala, the hippocampus, and the motor cortex (418, 420, 524).

An involvement of LTP-like processes in visual PL has been also suggested by Cook and Bear (101), who showed that a form of robust experience-dependent plasticity in V1 called stimulus-specific response potentiation (SRP) and consisting in amplitude increases in layer 4 VEPs after repeated presentation of a sinusoidal grating stimulus, is blocked by previous thalamocortical LTP induced with a theta burst electrical stimulation of the dorsal lateral geniculate nucleus.

In agreement with evidence in human subjects, we found a marked recovery of visual functions in amblyopic rats practicing our visual PL task; on the contrary, control animals practicing a visual associative task which did not induce LTP-like changes in V1, did not show any recovery. Visual PL, but not visual associative learning, is accompanied by a robust decrease of the inhibition-excitation ratio (28). We proposed that practice with visual PL through the amblyopic eye promotes recovery of visual functions via an LTP-like potentiation of synaptic input from the amblyopic eye on visual cortical neurons; this potentiation is likely to be favored by the lowered inhibition-excitation balance. Considering that the inhibition-excitation balance is also impaired during development in amblyopic human subjects and that excessive inhibition levels are involved in the degradation of their spatial vision abilities (280, 396), these results provide a strong rationale for future therapeutic attempts in humans based on a nonpharmacological manipulation of the GABAergic tone. In line with this, repetitive TMS (rTMS), a treatment increasing cortical excitability, transiently improves contrast sensitivity in adult amblyopes (482).

Finally, it is worth here to mention that caloric restriction, which is a mild environmental challenge, might play a key role in visual system plasticity, with the demonstration that a short-term protocol of food restriction starting in adulthood is able to renew the capability of recovery from amblyopia in long-term deprived animals, an effect associated with a reduction of GABAergic inhibition (469) **(FIGURE 2)**.

F. In Search of Enviromimetics

In addition to recovery from amblyopia, another classic paradigm of experience-dependent plasticity in the visual system is ocular dominance plasticity in response to MD. Exposure to enriched living conditions in adulthood is also able to reopen a sensitive period for this kind of plasticity, with the visual cortex of enriched monocularly deprived rats displaying a pronounced ocular dominance shift toward the closed eye, detectable both by VEPs and through single-unit recordings (32). While, also in this case, enhancement of plasticity is paralleled by a marked reduction of the inhibitory tone and an increase in the number of BDNF-expressing neurons in the visual cortex, a crucial role for the neurotransmitter serotonin in triggering the plastic changes elicited by exposure to EE has emerged **(FIGURE 2)**. Three sets of results point in this direction: *1*) EE elicits a twofold increase in V1 serotonin expression; *2*) infusion of the serotonin synthesis inhibitor PCPA (via minipumps) blocks plasticity in response to MD and completely counteracts the effects of EE on GABAergic inhibition and BDNF (33); and *3*) local infusion of serotonin into the visual cortex of adult nonenriched rats restores susceptibility to MD (319). Thus it is conceivable that the increased serotoninergic transmission in EE acts as the initial trigger for a chain of plastic changes including a decrease of GABA-mediated intracortical inhibition and, in parallel or in series, an enhancement of BDNF levels.

The role of serotonin as a master regulator of adult visual cortex plasticity has been also demonstrated in animals chronically treated with fluoxetine, a selective serotonin reuptake inhibitor (SSRI) widely prescribed in the treatment of depression and various psychiatric disorders. We found a complete recovery of V1 plasticity in adult animals subjected to a chronic treatment with fluoxetine delivered in the drinking water (318), together with a reduced GABAergic tone in the visual cortex; cortical diazepam administration totally prevented this effect (318). The reduction of inhibition triggered by fluoxetine provides a permissive environment for structural changes, such as the addition of new synapse-bearing branch tips (92), and the same treatment promotes an increase of BDNF expression in the visual cortex (318), paralleled by an epigenetic control leading to increased histone acetylation status at the BDNF gene promoter (319). In light of these promising results, fluoxetine appears to behave as a powerful enviromimetic (323), a drug that can be successfully exploited, alone or in combination with EE, to reproduce or to strengthen the positive effects elicited by the environment on brain health and plasticity. A critical permissive role for neuromodulatory transmitters on brain plasticity has been recently reported with the demonstration that Lynx1, an endogenous prototoxin which binds to the nicotinic acetylcholine receptor acting as a brake on cholinergic transmission, is upregulated after the closure of the critical period and that counteracting its action is sufficient to restore plasticity in the visual cortex of adult mice (339).

In addition to serotonin, GABAergic inhibition, and BDNF, it is likely that other mechanisms could underlie visual function recovery in amblyopic animals exposed to enriched conditions. Another possible candidate might be IGF-I; indeed, EE is associated with a transitory increase of IGF-I in the adult visual cortex and blocking IGF-I action prevents EE effects on adult visual cortex plasticity (317). Another mechanism through which EE enhances adult visual cortex plasticity is regulation of the brain chromatin status (146); indeed, epigenetic modifications, such as histone acetylation, have been recently implicated in the regulation of plasticity in the adult visual cortex (403, 458). At the extracellular level, it has been shown that infusion of an enzyme (chondroitinase ABC) that degrades extracellular matrix CSPGs, enhances adult V1 plasticity and reinstates visual acuity and binocularity in the mature cortex of amblyopic rats (393, 394). Since EE reduces the density of CSPG perineuronal nets in the visual cortex of enriched amblyopic rats (443), these changes can be critically involved in the reopening of cortical plasticity elicited by exposure to EE.

IV. ENVIRONMENT AND PLASTICITY IN THE AGING BRAIN

Aging is a physiological condition of life, accompanied by several changes in sensory, motor, and cognitive functions. There is considerable variance in the degree of cognitive decline associated with nonpathological aging, with some individuals maintaining strikingly active and effective intellectual abilities well into and even beyond their 90s. While some of the factors associated with graceful aging seem to be linked to the genetic endowment, many others are linked to environmental factors, such as the subject's lifestyle, and could be modifiable even in middle age to promote a successful aging. We shall now review the human and animal literature on the effects and mechanisms of action of environmental stimulation on cognitive decline with age and on age-related neurodegenerative dementia. We start by surveying the available literature on the link between neural plasticity processes and cognitive aging. Then, we discuss the impact of environment on age-related dementia, with particular attention to the concept of cognitive reserve and

to the role of lifestyle components as critical protective factors against dementia. Finally, we review the available literature focused on interventions based on physical exercise and cognitive activity on cognitive decline with age and dementia. Animal studies addressing the impact of EE on age-dependent neurodegeneration will be also surveyed, with a special focus on the underlying molecular and cellular factors.

A. Cognitive Aging and Neural Plasticity

The literature on age-related cognitive decline in humans shows that losses in cognitive performance are much greater for some tasks than for others (see Refs. 370, 371 for review). Decrements are typically slight in implicit memory tasks or verbal ability, while age-related losses are substantial in information processing speed and in tasks of declarative memory, particularly spatial memory and tasks requiring recollection of events and of the original context in which an event occurred. All these tasks involve the hippocampus and other medial temporal lobe structures. Also performance in inhibitory functions and in working memory tasks, relying on prefrontal cortex, declines with age; in particular, performance declines in those tasks that have high memory load and high demand on attention, which also deteriorates with age (371). Similarly, animal models of aging show a decline in memory tasks dependent on the medial temporal lobe and prefrontal cortex (see Refs. 26, 71, 130 for review).

Several papers have investigated the alterations in medial temporal lobe and prefrontal cortex which accompany normal aging and have discussed how these age-associated alterations might contribute to the selective cognitive impairments occurring with advancing age (see, for instance, Refs. 26, 52, 71, 209, 371 for review). Many of these studies point out that age-related changes in cognition cannot be accounted for by a generalized loss of neurons; indeed, in humans (366, 367, 413, 521), non-human primates (171, 331, 384), and rodents (330), significant reduction of cell number in the hippocampus and neocortex is not typical of normal aging. There are, instead, age-related reductions in synaptic density and neuropil, resulting in reduction in volume of specific brain structures, but not a general decrease in the number of neurons. In the human healthy brain, $<$10% of neurons are lost over the range 20–90 yr (26, 52, 71). There are, however, notable exceptions: in aged primates, neuron number in prefrontal area 8A undergoes a 30% reduction which is evident in all layers; this reduction significantly correlates with the extent of the impairment in a working memory task. In contrast, prefrontal area 46 shows, in the same animals, conservation of neuron number; also the damage of cholinergic input differs between these two prefrontal areas (465). We take the opportunity to underline something that might seem obvious but which is important to bear in mind. As in humans it is important to distinguish between age-related changes in the brain in subjects not affected by neurodegenerative diseases and subjects who are, the best animal models to investigate normal aging are aged animals, not transgenic animal modeling neurodegenerative diseases.

At the level of neuronal morphology, investigations on dendritic branching and density of dendritic spines show that also age-associated morphological alterations are region-specific: aging seems to affect morphology of prefrontal cortex neurons more than that of hippocampal neurons (see Ref. 71). As far as neural plasticity is concerned, normal aging causes evident changes at multiple levels, both at a basic physiological level, such as for the well-documented changes in Ca^{2+} conductance and homeostasis (89, 265) which might indirectly affect neural plasticity, and directly at the level of plasticity mechanisms related to declarative memory processes, such as hippocampal LTP. Hippocampal LTP is altered in aged animals at the level of both induction and maintenance, with maintenance most severely affected (see Ref. 71 for review). Since maintenance of LTP requires gene transcription and protein synthesis, it does not come as a surprise that these processes are altered in aged animals (see Ref. 71). Also in humans gene expression changes have been documented in the course of normal brain aging, with gender differences (52). Aging strongly reduces hippocampal neurogenesis across several species (see Refs. 11, 12, 229–231). In humans, indirect evidence for reduced neurogenesis in aged subjects comes from the study of Knoth et al. (245) and by volumetric reductions in the hippocampal formation found in aged subjects (16, 463). Diminished neurogenesis with age could be the result of CNS-derived factors and blood-borne factors extrinsic to CNS, as recently suggested by Villeda et al. (513). A more direct evidence has been recently obtained for an age-related reduction of neurogenesis in human hippocampus (468).

In animal models of physiological aging, age-related alterations in hippocampal LTP induction or maintenance are in good correlation with the degree of spatial memory impairment and with the stability of hippocampal place cell fields (see Ref. 71). Recent evidence has indicated that also epigenetic mechanisms related to neural plasticity might be altered in aged mice. Peleg et al. (379) found that during contextual fear conditioning learning, aged mice exhibited a specific deregulation of histone H4 lysine 12 (H4K12) acetylation accompanied by a failure to start hippocampal gene expression pattern normally found in correspondence to memory consolidation. This was in very good correlation with behavioral data showing a deficit in long-term fear memory. Interestingly, restoration of physiological H4K12 acetylation reinstated the pattern of gene expression normally found in the hippocampus following learning and led to recovery of cognitive performance.

B. Compensatory Plasticity in Aging

In parallel to diminished neural plasticity, there are numerous examples of what can be considered compensatory plasticity during the aging process. This shows up mostly in terms of a larger and more elaborate pattern of activation of brain areas, and in particular of the prefrontal cortex, in aged with respect to young subjects performing the same task; interestingly, this more extensive activation correlates with better performance in the elders (see Ref. 371 for a recent review). As an example, Cabeza et al. (72) studied prefrontal cortex activation during recall and source memory of recently studied words in younger adults, low-performing older adults, and high-performing older adults. They found that old subjects with a good performance showed additional activity in the left prefrontal cortex with respect to young subjects; old subjects with poor performance did not. Is this additional activity important for the better performance of old subjects? To answer this question, rTMS has been used to transiently disrupt prefrontal cortex function. In the study by Rossi et al. (430), rTMS was applied to left or right dorsolateral prefrontal cortex of young and old subjects during the encoding phase of a recognition memory test, which is while subjects observed and memorized a series of pictures, and during the retrieval phase of the test, which is while subjects judged whether the presented pictures were new or already seen. The results indicated that accuracy of memory retrieval in young subjects was more affected when rTMS was applied to the right than to the left hemisphere during retrieval, while in old subjects accuracy of retrieval was equally affected by application of rTMS to either hemisphere; this strongly suggests that in young subjects the activity of the right dorsolateral prefrontal cortex was necessary and sufficient to obtain a good performance in the task, while in old subjects activity of both right and left dorsolateral prefrontal cortex is necessary for successful performance in the recognition memory task.

Similar results to those described here for memory have been found for linguistic (532) and motor abilities (201); interestingly, one of the additional brain areas recruited by elders with good performance in the linguistic task is an area activated in young subjects in situations of particularly complex sentence processing, which stresses working memory demands. This additional activation, which young people use in challenging situations, would compensate for the lower activation in the core left hemisphere posterior language areas found in aged people. The result is as good a performance in elder as in young subjects. Thus the aging brain can maintain a relatively high level of performance through neural plasticity processes, optimizing goal attainment with the available resources. Park and Reuter-Lorenz (371) point out that compensatory plasticity in the form of more elaborate patterns of brain area activation is not unique to aging but that it is the brain's response to cognitive challenge; it is more likely to find a more elaborate pattern of brain area activation in aging brains even for simple tasks simply because tasks which for young brains result to have a low level of complexity bring forth significative cognitive challenge for older brains (371). Thus enhancing neural plasticity in old age, both that underlying learning and memory and that underlying compensatory activation, might benefit cognitive performance in elders through multiple mechanisms.

C. From Normal Age-Related Cognitive Decline to Dementia

The existence of a long transition phase between normal aging and dementia which is likely to extend to presenile ages is now hypothesized. Indeed, converging evidence from the experimental and clinical literature indicates that moderate levels of cognitive impairment and the presence of subtle cerebral alterations, detectable with techniques such as structural and functional neuroimaging, precede of several years the clinical onset of the disease (113, 167–169, 226, 392). This stage is referred to as mild cognitive impairment (MCI). MCI affects a vast number of people and is characterized by objective deficits in one single domain (e.g., memory) or multiple domains of cognition, which do not yet configure as overt dementia. These impairments are objectivated by appropriate neuropsychological tests (385–388). The rate of yearly progression to dementia of MCI subjects is much higher than in the non-MCI elderly; in particular, the amnestic subtype of MCI (aMCI) may represent a prodromal form of Alzheimer's disease (AD) (368, 387, 450). However, a good proportion of MCI subjects not only do not develop dementia, but can also recover from the initial slight impairments that characterize them as MCI subjects (162, 220, 386, 387, 462).

Also, in animal models of AD, deficits in synaptic density and plasticity and cognitive impairment precede the presence of characteristic anatomical hallmarks of AD, such as beta amyloid (Aβ) deposits and neurofibrillary tangles (see, for instance, Refs. 112, 221, 277, 455); onset of cognitive deficits correlates well with the presence of diffuse Aβ oligomers, which are currently hypothesized to be the first pathogenic agents in AD and have been shown to impair neural plasticity and memory when administered to wild-type animals (see, for instance, Refs. 277, 284, 455). This supports the existence of a preclinical phase in the path toward dementia in which deficits in synaptic density and plasticity are the principal alteration.

On the basis of epidemiological studies in humans, risk and protective factors for developing dementia with age have been pointed out, which include genetic factors, such as the presence of the apolipoprotein E ε4 allele (APOE4) or familiarity for the disease, and lifestyle factors, such as being engaged in cognitively stimulating and social activities and practicing physical exercise, key components of an "en-

riched environment" (e.g., Refs. 158, 254, 270, 316, 395). In agreement with studies in humans, it has been shown that physical exercise and EE result in better cognitive performance and potentiation of neural plasticity in aged animals and in animal models of neurodegenerative diseases (see Refs. 355, 356). Thus transition to clinical manifestation of dementia seems to have a strong environmental component. Historically, the first environmentally derived protective factor described has been the "cognitive reserve."

D. The Concept of Cognitive Reserve and Its Status of Protective Factor Against Severe Cognitive Decline With Age and Dementia

The concept of cognitive reserve has been proposed to explain the discrepancy between the degree of brain damage and the extent of clinical manifestations (see Ref. 473). It postulates that subjects with a greater cognitive reserve can tolerate a greater extent of brain damage before showing significant cognitive impairment. Cognitive reserve is an active reserve and posits enhanced complex mental activity and high cognitive functioning as protective factors against major age-related cognitive decline and dementia (see Refs. 356 and 473 for review).

Among the factors possibly contributing to cognitive reserve development, education, occupational attainments, and leisure activity have been shown, by epidemiological studies, to provide reserve capacity against the effects of aging and disease on brain function. This hypothesis has been supported initially by studies showing a strong variability in the relationship between the severity of brain pathology and clinical manifestations (see Refs. 159 and 473 for review). More recently, additional evidence has been provided by neuroimaging methods: functional imaging in vivo such as PET, which correlates with AD neuropathology, and is an indicator of disease severity and progression (64, 333), has shown that for a given level of cognitive impairment, highly educated patients exhibit a stronger alteration in cerebral metabolic activity and blood flow than subjects with lower education (9). Recently, Garibotto et al. (167) showed a significant correlation between higher education/occupation and lower cerebral metabolic activity in specific brain areas in AD patients and in aMCI subjects which later converted to AD (aMCI converters); there was, however, no correlation between education/occupation and cerebral metabolic activity in the same areas for aMCI nonconverters and healthy controls. This led the authors to suggest that "education and occupation may be proxies for brain functional reserve" and that exploitation of this reserve is already ongoing in preclinical phases of AD.

As for all brain functions, cognitive reserve is likely to have *1*) a genetic component, providing individuals with a different endowment in terms of brain circuitry which might also explain the higher educational and occupational attainments; *2*) a purely environmental component, that is, the EE contributing factors provided by early environment, higher education and engaging occupational and leisure activities, which might positively affect synaptic connectivity, synaptic plasticity, compensatory plasticity, and hippocampal neurogenesis, allowing better resilience/compensation for the effects of aging and pathology; and *3*) an interaction between the two components (see Ref. 473). It has to be underlined that the presence of a possible genetic component in the construct of cognitive reserve might constitute a confounding factor in that it might affect both the educational and occupational attainment and the cognitive decline, without these two factors being causally related. This is particularly important to consider since the studies providing support for the cognitive reserve hypothesis and in particular for the protective effects of education (see Ref. 498 for a recent review) are epidemiological. Another possible confounding factor could be the presence of a preclinical state in middle age, which compromises both occupational attainment and cognitive maintenance in older ages.

One of the first studies in support of the cognitive reserve hypothesis is by Katzman (227), who has shown that subjects with high levels of education have a 5-yr delay in dementia onset. The Nun study (417, 495, 496) has adopted a different research design, revealing that the presence of elevated levels of ideation and creativity, as estimated from youth autobiographies written at entrance in the convent, correlated with maintenance of good cognitive capacities in old age: nuns well in their 80s who had an intact memory were those with the highest ideation capacity as estimated by the youth autobiographies. This was considered a combination of the effects of a rich experience, particularly school and linguistic education, and possibly of a genetic component, the latter suggested by the presence of lower neurofibrillary tangles and amyloid plaques in high-idea-density than in low-idea-density nuns. It has to be said that, in a perspective of disease modification effects of EE suggested by animal studies (see below), those anatomical findings might not necessarily point to a genetic component.

Another group of studies has shown that engaging in a variety of cognitively stimulating leisure activities in middle and old age is also associated with a significant reduction of dementia incidence. Among the studies that have produced evidence in this sense, there are those of Valenzuela and Sachdev (500, 501), two studies of meta-analysis on a total of 29,000 and 47,000 individuals, respectively, which found that individuals with higher levels of education, occupation, or engagement in complex cognitive activities were at 46% lower risk for incident dementia than those with low levels. It is interesting, as Valenzuela and Sachdev point out, that for middle- and old-aged persons, being presently engaged in complex patterns of mental activity results a significant protective factor even after controlling

for the effects of past factors (education, occupation, baseline cognition) and for cardiovascular risk factors (498).

A very interesting study is that of Carlson et al. (77), who examined male twins pairs who differed for dementia diagnosis or for age at dementia onset. The results show that "participation in a range of cognitively and socially engaging activities in midlife reduced risk for dementia and AD in twins discordant for onset, particularly among monozygotic twin pairs at elevated genetic risk, and might be indicative of an enriched environment" (77). Thus cognitive reserve might be compared with the effects of an enriched environment, with components typical of childhood and youth (education), others typical of adulthood and early old age (occupational type and attainments), and others shared by all ages (cognitively stimulating leisure activities and socially engaging activities). Higher educational and occupational attainment and leisure activities seem to independently contribute to cognitive reserve (see Refs. 473, 498). These findings have been confirmed by Yaffe et al. (537), who followed the time course of cognitive status of 2,509 well-functioning black and white elders enrolled in a prospective study for 7 years. Participants were classified as cognitive maintainers, minor decliners, or major decliners according to the slope of the curve describing cognitive score change with time. Characteristics of the cognitive reserve, such as education level, literacy, and lifestyle, emerged as significant predictors of being a maintainer versus a minor decliner. Of particular interest is the study by Paillard-Borg et al. (365) which, in a 9-yr follow-up study, showed that an active lifestyle including mental, physical, and social activities delays the onset of clinical condition in old subjects; when the three types of activities are combined to generate a single index, it emerges clearly that the broader the spectrum of participation in the activities, the later the onset of disease, in accordance with the concept of enriched environment.

Very few epidemiological studies attempted to explore, in humans, the mechanisms underlying the effects of being engaged in complex mental activity on dementia risk, and the results are not always in complete agreement. Valenzuela et al. (502) determined whether individual differences in complex mental activity over the lifespan were linked to differences in the rate of hippocampal atrophy, finding that this was the case, with higher level of complex mental activity associated with lower rate of hippocampal atrophy. They suggested that high mental activity might be exerting a neuroprotective action in medial temporal lobe and that this might explain the lower dementia incidence associated with it in epidemiological studies. In a more recent study, however, with a 14-yr followup of a large cohort of subjects aged >65 years, no evidence for hippocampal neuroprotection was found. Instead, men and women both exhibited significantly greater neuronal density, as well as correlated increases in cortical thickness in prefrontal area 9 linked to cognitive lifestyle, consistent with a compensatory process.

Landau et al. (263) assessed whether the level of cognitive (reading, writing, and playing games) and physical exercise was associated with the extent of Aβ deposition in healthy elders; Aβ burden was determined using the 11-labeled Pittsburgh Compound B and PET. The subjects were followed for 6 years. The results showed that lower Aβ burden was found in subjects more engaged in cognitively stimulating activities, particularly during early and middle life. Strikingly, when subjects were divided in percentiles with respect to the level of cognitive activity, Aβ burden in subjects within the highest tertile was comparable to that of young controls, whereas in subjects within the lowest tertile it was comparable to patients with AD. Thus there seems to be a direct correlation between cognitive activity and Aβ burden, suggesting that lifestyle factors might prevent or slow down Aβ deposition.

As already discussed, great help towards understanding mechanisms underlying the effects of experience on the human brain comes from animal models. In the case of cognitive reserve, however, it is intrinsically impossible to reproduce in animal models different levels of education or occupational attainement. Some analogies can be drawn from the effects on the aging brain of EE paradigms starting from a young or adult age (389). Indeed, a prolonged and successful school experience and engaging in satisfactory and rewarding work activity might be considered akin to an "enriched environment," although EE contains a component of physical activity not necessarily present in subjects with a high cognitive reserve.

As an example, exposure to EE from weaning or juvenile ages to old age improves prefrontal cortex-dependent working memory and spatial memory in rats (466). In addition, Diniz et al. (122) found improved spatial memory and increased number of astrocytes in the molecular layer of the hippocampus in mice reared in EE from weaning to old age. The beneficial effects of EE have been attributed to increased levels of BDNF, enhanced neuroplasticity, and increased hippocampal neurogenesis (311).

EE has been found to have beneficial effects in animal models of neurodegenerative diseases, and the continuously growing literature in this field has been recently reviewed by Nithianatharajah and Hannan (435). These studies have shown that EE can enhance cognitive performance, delay the onset of the disease and slow down its progression, acting on neural plasticity processes and on disease-related cellular and molecular factors. EE in mouse models of Huntington disease (HD) was the first demonstration of EE effects in a genetic model of brain neurodegenerative disorder (503). Subsequently, EE and physical exercise have been shown to exert beneficial effects in models of HD, AD, and

Parkinson's disease (see Refs. 355 and 416). We shall concentrate on early EE effects on AD models in relation to the cognitive reserve hypothesis.

Many studies have employed protocols of EE starting before the onset of cognitive deficits, thus modeling the effects of cognitive reserve in delaying the onset of clinical manifestations. There is general agreement that EE has beneficial effects on the onset of cognitive deficits in animal models of AD (see Refs. 355, 416). There is, however, a debate on the underlying mechanisms, in particular regarding EE effects on Aβ metabolism. For instance, Lazarov et al. (273) found that a protocol of EE from 3 wk to 6 mo of age resulted in pronounced reductions in cerebral Aβ levels and amyloid deposits, compared with animals raised under "standard housing" conditions in male mice coexpressing Familial Alzheimer's Disease (FAD) mutations [human PS1ΔE9 and a harboring a human Aβ domain and mutations (K595N, M596L) linked to Swedish FAD pedigrees (APPswe)]. In addition, the activity of an Aβ degrading enzyme, neprilysin, is higher in the brains of EE mice in correspondence with lower Aβ burden. More recently, Hu et al. (213) found that EE from P21 to P90 enhanced hippocampal neurogenesis in male APPswe/PS1ΔE9 mice to levels comparable to those of wild-type animals, reduced hyperphosphorylated tau, and oligomeric Aβ levels in the hippocampus and cortex of enriched mice and significantly enhanced hippocampal LTP, without notable alterations in basal synaptic transmission. Reduction in Aβ load following exposure to running from 1.5 to 2.5 mo has been found also in male and female TgCRND8 mice (3). Berardi et al. (48), in a mouse model for NGF deprivation induced AD-like neurodegeneration, the AD11 mice, found that EE starting from 2 mo of age, that is before the onset of behavioral deficits in AD11 mice, and ending at 7 mo of age, prevented, both in males and females, the onset of visual recognition and spatial memory deficits, reduced the presence of Aβ burden, and rescued the cholinergic deficit present in these animals. This study also addressed the long-term effects of EE exposure: a group of EE AD11 mice was left out of EE after completion of the cognitive tests up to 12 mo of age; these AD11 mice exhibited a better memory than non-EE AD11 mice of the same age, and did not differ from 12-mo-old wild-type mice.

These results point to a strong effect of early EE on Aβ processing: this could be due to alterations in Aβ catabolism and sequestration in enriched animals, as proposed by Lazarov et al. (273), to the processing of the amyloid precursor protein, as suggested by Adlard et al. (3), and/or to the direct effects of IGF-I, which is known to be increased in enriched animals, on Aβ metabolism and clearance (80, 170). On the other hand, Arendash et al. (17) have shown in SweAPP aged mice that EE improves cognition but does not reduce Aβ deposition, and Jankowsky et al. (223) have shown that EE has some positive effect on spatial memory deficits in female transgenic mice expressing SweAPP and/or exon 9 deleted presenilin-1, but this is accompanied by an increase of Aβ42 levels. This discrepancy on EE effects on Aβ might be due to differences in enrichment protocols, but there is also another possibility to explore, that is, possible effects of EE or running on diffuse Aβ oligomers, not investigated in the studied quoted above. For instance, Berardi et al. (48) found a lack of correlation between the presence of Aβ clusters in the hippocampus and behavioral performance in AD11-EE mice. This might be due to the presence of a critical threshold of Aβ accumulation in the hippocampus below which performance is no longer dependent on the extent of Aβ deposits; alternatively, given the recent data already mentioned before [see, for instance, Shankar et al. (455)] showing that small, soluble oligomeric forms of amyloid-β inhibit hippocampal LTP and impair cognitive functions prior to the appearance of amyloid plaques, it is likely that diffuse Aβ correlates best with cognitive performance, particularly in the early stages of the disease (277, 455).

A very recent paper addressed the protective effects of early exposure to EE on the disruption of hippocampal LTP by acute infusions of Aβ oligomers (283). A few-week exposure to EE enhanced hippocampal LTP, preventing its inhibition by Aβ soluble oligomers extracted from human AD patient cortex. Interestingly, a possible mediator of this protective EE effect was suggested to be the activation of β-adrenoceptor signaling.

E. Beneficial Effects of Physical Exercise on Age-Related Cognitive Decline and Dementia

In the last 12 years, it has become evident that exercise can attenuate normal age-related cognitive changes and deficits and also reduce the risk for MCI and dementia.

Among the earliest studies that have followed the epidemiological approach to investigate this relation, there are the Canadian Study of Health and Aging (270) and the studies of Weuve et al. (523), Podewils et al. (395), and Abbott et al. (1), mostly employing subjective measures for the level of physical exercise and finding a positive correlation between physical exercise and maintenance of good cognitive level with age. Barnes et al. (27) employed both subjective and objective measures of cardiorespiratory fitness in a sample of 349 individuals over 55 yr of age followed for 6 yr. The results show that the positive correlation between fitness and cognitive status was higher for the objective than for the subjective measure of fitness. All these studies point out that the higher and more varied physical activity, the lower cognitive decline and dementia incidence. The estimated reduction in the risk for dementia varies from a study to another, but most studies estimate this reduction around 50%. The Podewils et al. (395) study strengthens also the

presence of a gene × environment interaction: physical activity did not result in a protective factor against the probability to develop dementia for subjects carrying the APOE4 allele as it was for the noncarriers (for a review, see Ref. 255).

More recently, the already mentioned Yaffe et al. (537) study included, among the significant predictors of being a maintainer versus a minor decliner, engaging in weekly moderate to vigorous exercise. Bugg and Head (70) found that higher levels of physical exercise benefited both the frontal and the mediotemporal lobe, resulting in reduced atrophy. In addition, Eltgen et al. (134) in a community-based prospective cohort study in which the subjects were followed for 2 years, found that participants with moderate or high physical exercise levels at baseline had a significant reduction of cognitive impairment. Baker et al. (24) showed that in elders with glucose intolerance, a risk factor for AD, aerobic exercise improved cognition. Buchman et al. (69) assessed total daily physical activity for up to 10 days with actigraphy from 716 older individuals without dementia, characterized them and then followed these subjects for 4 years. They found that a higher level of total daily physical activity, even after taking into account other protective or risk factors, was associated with a reduced risk of AD. Woodard et al. (534) investigated the effect of self-reported physical and cognitive activity on hippocampal volume and semantic processing brain activation in 78 cognitively intact older adults followed for 18 mo, examining whether possession of the APOE4 allele could reduce the effect of physical or cognitive activity on hippocampal structure or function. The results show that cognitive activity alone or in combination with baseline hippocampal status were not predictors of the degree of cognitive decline. In contrast, physical activity reduced the risk of cognitive decline, but only in APOE4 carriers. These results are at variance with those of Podewils et al. (380) in that they suggest that increased leisure time physical activity is associated with reduced probability of cognitive decline also in APOE4 carriers. Baker et al. (23) found that physical exercise strongly modulated the negative effects of a high saturated fat/high glycemic index (HIGH) diet on Aβ levels in cerebrospinal fluid of elders; in particular, increased physical activity attenuated the effects of the HIGH diet on cerebrospinal fluid Aβ.

Given the relation between Aβ, neural plasticity, and cognition suggested by animal studies, these results would suggest that physical exercise could directly impinge on Aβ clearance. Animal studies confirm this and provide a mechanism of action via IGF-I. IGF-I, which is increased by physical exercise, favors clearance of Aβ from the brain, possibly enhancing the transport of Aβ-carrier proteins into the brain and elevating the fraction of Aβ bound to them and transported across the blood-brain barrier into the liquor; administration of IGF-I to aged rats decreases Aβ content in the brain and increases it in the cerebrospinal fluid (79, 168, 350).

A more detailed discussion of the possible factors underlying the effects of physical exercise on the aging brain is left to the next section, dealing with the effects of interventions based on physical and cognitive exercise both in aged humans and animals. One last consideration on the epidemiological evidence for a contribution of physical exercise to cognitive maintenance in elders is necessary. Despite the fact that most of the correlational studies found a positive relationship between physical activity and cognition in elders, it has to be noted that some have not (255, 531, 538). At present, it is difficult to understand which factors could moderate the influence of physical activity on age-related cognitive decline: possible factors include the distinction between aerobic and nonaerobic physical activities, the use of self-report versus objectively measured levels of physical activity, the cognitive domains investigated and the tests employed, the age of participants at initial and final assessment, and a lack of assessment of genetic factors.

F. Effects of Interventions Based on Physical Exercise and Cognitive Activity on Cognitive Decline With Age and Dementia

The last few years have seen an increasing number of studies devoted to assessing the effects of cognitive activity and physical exercise on age-related decline via intervention approaches. Among the first studies which have followed this approach are those of Colcombe et al. (98) and Kramer and Erickson (254). In these studies, relatively small (30–40) groups of nonpathological elders underwent physical training consisting of three weekly sessions of controlled aerobic physical exercise for a period of a few months. Cognitive performance was assessed before and after the training and in some cases was correlated with cortical activation, evaluated with fMRI. The results indicate that cognitive performance was ameliorated in those subjects who performed aerobic training, in good correlation with the level of cardiovascular fitness and the pattern of brain activation (see Ref. 255). A Cochrane comprehensive survey (13, 14) specifically reviewed the evidence that aerobic fitness is necessary for improved cognitive function: it concluded that "aerobic physical activities which improve cardiorespiratory fitness are beneficial for cognitive function in healthy older adults," but pointed out that "the data are insufficient to show that the improvements in cognitive function which could be attributed to physical exercise are due to improvements in cardiovascular fitness, although the temporal association suggests that this might be the case, and that larger studies are required."

More recently, Williamson et al. (528) reported the results of a pilot study (LIFE study) estimating the relative impact

of physical activity, aerobic (walking), strength, balance, and flexibility exercises on variations in cognitive status over a 1-yr period in elders. Sedentary persons ($n = 102$) of 70–89 yr of age were randomized to an intervention group of moderate-intensity physical activity or to a group undergoing health education. Group differences did not reach significance, but improvements in cognitive scores were associated with improvements in physical function.

Erickson et al. (131) showed, in a randomized controlled trial in older adults, that aerobic exercise training leads to improvements in spatial memory and is accompanied by a 2% increase in anterior hippocampal volume, which reverses age-related volume loss. Caudate nucleus and thalamus volumes were unaffected by the intervention, showing that exercise effects are structure specific. They also demonstrated that increased hippocampal volume is associated with greater serum levels of BDNF. As we have seen, BDNF is a mediator of neurogenesis in the hippocampal dentate gyrus in response to physical exercise and EE (103, 429). Thus these two randomized control trials of aerobic exercise in nondemented seniors were associated with increased cortical volume (432). It has to be underlined that in a long-term (9 yr) study, the average weekly physical activity (walking) reported by healthy adults at baseline was positively associated with neocortical and hippocampal volumes (see Ref. 4). We may conclude that voluntary physical exercise contributes to build a cognitive reserve even when undertaken in middle and old age.

The literature on the effectiveness of cognitive intervention on cognitive aging was reviewed in 2009 by Valenzuela and Sachdev (498), who found only seven studies qualifying as randomized control trials. A strong effect size was observed for cognitive exercise interventions compared with wait-and-see control conditions. Randomized control trials with follow-up greater than 2 yr did not appear to produce lower effect size estimates than those with less extended follow-up. The conclusion was that, despite the quality of reporting of trials being in general low, cognitive exercise training in healthy older individuals produced strong and persistent protective effects on longitudinal neuropsychological performance.

One notable more recent study on cognitive training, though not performed specifically in aged subjects, is that by Owen et al. (363), which put to the test the effects of computerized brain trainers. The central question of the paper was whether the effects of training on specific cognitive tests could transfer to other untrained tasks or lead to a general improvement in cognitive status. The results indicate that training did improve performance in every cognitive task in which subjects practiced, but "no evidence was found for transfer effects to untrained tasks, even when those tasks were cognitively closely related." This underlines the importance of the concept of enriched environment as the driver of enhancement of neural plasticity and cognitive processes. In particular, it emphasizes the unique nature of EE as a "multidomain training" not restricted to a single modality, process, or function.

Very recently, studies are being performed on the effects of training, cognitive or physical, on MCI or AD subjects. Lautenschlager et al. (271), in a study on adults over 50 with subjective memory impairment, found that 6 mo of physical activity resulted in a modest improvement in cognition assessed in a followup 18 mo after the end of the intervention. Baker et al. (24) investigated the effects of a 6 mo program of aerobic exercise in 33 adults (17 women) with a MCI ranging in age from 55 to 85 yr. They found gender-specific effects on cognition, with older women benefiting on a larger number of executive function tests than men, which had a limited benefit.

In addition, physical exercise interventions have been shown to modulate the effects of diet on Aβ cerebrospinal fluid levels in MCI subjects. A healthy diet produced the strongest effects on Aβ when paired with physical exercise (23). Exercise and diet may thus interact in modifying the risk of AD. This underlines the possibility that factors such as physical exercise, cognitive activity, and other lifestyle factors might be additive in reducing the risk of severe cognitive decline and dementia, as suggested also by Paillard-Borg et al. (365).

All this evidence makes a strong rationale towards the effectiveness of the combination of physical and cognitive training in interventions attempting to ameliorate the cognitive status and to counteract disease progession in subjects in the preclinical stage of dementia. A randomized trial on the effects of a combined physical and cognitive training on cognitive decline, brain volume, and cerebral function in MCI subjects is underway in Italy, with the joint cooperation of two Institutes of the National Research Council (IN-CNR and IFC-CNR, Pisa) and under the coordination of Lamberto Maffei and Eugenio Picano.

Animal studies employing the EE paradigm are particularly suitable to investigate the mechanisms underlying the effects of interventions of physical exercise and complex mental activity in aged humans (see Refs. 229, 255, 356). As EE starting from young or adult ages can be used as a model for the protective effects of cognitive reserve, EE starting in elderly animals can be used as a model for interventions based on physical and cognitive training in aged humans.

Most of the studies have been conducted in aged rodents, but EE has been found to provide cognitive benefits also in other aged mammals (332, 355, 399, 416, 499). Positive effects of EE on cognitive processes have been found both for hippocampal-dependent and -independent learning and memory (47). These beneficial effects have been related to

EE action on neurogenesis, neurotrophic factors (BDNF), IGF-I, synaptic plasticity, and neurotransmitter systems discussed in the previous sections (see Refs. 261, 356, 360, 437, 498).

Some of the mechanisms of action of EE on age-related decline in plasticity are directed to cellular factors specifically altered by aging, such as Ca^{2+}-dependent conductance. As previously outlined, a consistent finding across several species is that aged animals exhibit an increase in the Ca^{2+}-dependent, K^{+}-mediated afterhyperpolarization (AHP), which might contribute to plasticity deficits. Kumar and Foster (260) tested the hypothesis that EE might reduce the amplitude of AHP in aged rats, obtaining positive results, consistent with the idea that EE can ameliorate senescent hippocampal physiology. Also, neurogenesis in aged hippocampus (453) and cortical vascularization (405), possibly linked to EE effects on VGF, are increased by EE.

Recently, an example of the beneficial effects of EE on aged brain plasticity has been provided: the effects of a short (three weeks) exposure to EE in aged (22–23 mo of age) rats were tested in a model of visual cortical plasticity (447). The results showed that this brief period of EE was sufficient to reactivate ocular dominance plasticity, with no difference with the reactivation found in adult rats (32). As in adult rats, a marked reduction in intracortical GABAergic inhibition and a remodeling of extracellular matrix accompanied this effect, suggesting that the same plasticity mechanisms were at work in mediating EE effects in adult and aged rats (447). Whether EE is also able to reverse the modifications induced by aging on the epigenetic mechanism underlying neural plasticity (379), as found for those constraining cognitive capacities in the neurodegenerating brain (179), is not known.

A particularly striking effect of EE and physical activity in aged animals is that on the levels of hippocampal neurogenesis (recently reviewed in Ref. 229). As outlined in the Introduction and in Chapter III, there is general agreement that hippocampal neurogenesis is central to the functionality of the hippocampus and in particular new neurons would be crucial for dentate gyrus contribution to pattern separation (348), a critical mechanism for reducing potential interference among similar memory representations. In parallel to the well-known decrease of neurogenesis in aged animals, it is beginning to emerge that old animals exhibit a less efficient pattern separation, particularly in the spatial domain. This decreased efficiency in spatial pattern separation may be a critical processing deficit that could be a contributing factor to spatial memory deficits and episodic memory impairment associated with aging [for a recent review, see Holden and Gilbert (209)]. Kempermann et al. (230) found that, given the extremely low baseline level of aged rats, the relative increase due to EE was even larger than in younger animals, although the overall absolute activity-induced proliferation of precursor cells remained lower than in young animals. The increase in neurogenesis due to environmental factors could contribute both to reduce the age-related decline in hippocampal volume, particularly evident in the dentate gyrus (463), and to improve dentate gyrus function in pattern separation. Of particular interest, also in relation to intervention in humans, is the finding that the effects of exercise and EE on adult neurogenesis seem to be additive (135): sequentially combining the effects of physical activity on precursor cell proliferation with the survival promoting effects of EE resulted in a much greater effect with respect to that caused by EE or exercise alone.

It must be underlined that there is a great variability in the literature both in the age of onset and in duration of EE exposure. A sort of dose-dependent effect of EE on spatial memory in aged rats was found by Bennett et al. (47): aged animals continuously living in an enriched environment performed better than animals exposed to 3 h/day of enrichment during the same period. Exposure in adulthood seems sufficient for EE to positively affect cognitive decline in old age (see Ref. 389). Kobayashi et al. (247) found that short-term (3 mo) or long-term (24 mo) EE had beneficial effects both in 11- and 22-mo-old rats and observed that in the more aged rats the effects of the longer EE period were more pronounced. However, Freret et al. (161) found in female Naval Medical Research Institute (NMRI) mice that EE had to be initiated before the age of 17 mo (median lifespan, i.e., the age corresponding to the survival of 50% of the population in this strain) to improve spatial learning and reverse the age-related impairment of basal glutamatergic neurotransmission in CA1 hippocampal slices. Qiu et al. (404) exposed 14-mo-old (middle-aged) female and male rats to EE for 4 mo. Female rats housed in EE showed improved performance in the Morris water maze. The total length and total volume of the myelinated fibers in the hippocampus of female and male enriched rats were significantly increased, respectively, compared with female and male control rats. Thus 4 mo of EE from middle age was sufficient to increase myelinated fiber volume and, in a gender-dependent way, spatial memory. In addition, it has been reported (261) that aged (20–22 mo) male rats assigned to EE for 10–12 wk showed enhanced spatial discrimination learning and memory consolidation compared with controls. Examination of senescent hippocampal physiology revealed that EE reversed age-related changes in LTD and LTP. Rats in EE exhibited an increase in cell excitability compared with the other two groups of aged animals.

The positive effects of EE starting in old age on cognitive performance and brain pathology have also been assessed

in models of neurodegenerative diseases and have been reviewed by Nithianantharajah and Hannan (355), evidencing how even a late starting EE can be beneficial. Unpublished work from our laboratory goes in this direction, showing that exposure to EE after cognitive deficits are already evident determines a complete rescue in AD11 mice, despite the fact that preexisting Aβ pathology was not removed. BDNF could be among the possible factors mediating this rescue effect. It has been shown that a reduction in BDNF levels is present early in the progression of AD (381, 391). Aβ is likely to contribute to a reduction in BDNF signaling (380). Invasive BDNF administration has been recently used in animal models of AD with very good results on memory deficits and synaptic density (61, 346), and work from our laboratory provides evidence for beneficial effects of noninvasive administration (Berardi et al. *FENS Abstr* 4: 217.3, 2008). Given the known effects of EE and physical exercise on BDNF (103, 437), this neurotrophin could be one of the mediators of EE effects in AD models. Interestingly, BDNF could act on the production and/or clearance of Aβ, but it is by now clear that neurotrophins can improve learning and memory in AD models in an Aβ-independent manner (61, 346) likely acting on synaptic plasticity or, possibly, on neurogenesis (82, 199).

A particularly striking work on EE effects in mice models of neurodegenerative pathologies is that by Fischer et al. (146), who examined the beneficial effects of EE in a mouse model of aggressive and extensive neurodegeneration, the p25 transgenic mouse, which allows temporally and spatially restricted induction of neuronal loss. The p25 protein has been implicated in various neurodegenerative diseases, including AD (105). The authors had previously demonstrated that, upon induction of the p25 transgene in adult mice, neurodegeneration is triggered, and animals also display both learning and memory impairments (145). Six weeks after switching the transgene on, mice are not only unable to form new memories but they are also unable to retrieve memories acquired before the transgene was switched on. The authors have used this model system to assess whether EE has beneficial effects in this transgenic animal model (146). Six weeks after induction of p25, when anatomical and functional deficits are well established, the authors transferred the animals into an EE for 4 wk. Surprisingly, the authors found that this rescued the mice's ability to form new memories (i.e., the mice learned a new fear conditioning and a new spatial task) and also allowed to reestablish access to remote memories learned prior to brain degeneration, despite the fact that the neuronal loss did not recover. It is important to note that the newly formed memories were hippocampus dependent, while remembering the remote memories likely involved accessing neocortical networks, as the mnemonic traces would have been progressively "transferred" from the hippocampus to the neocortex over time. Indeed, while recall of recent memories activates the hippocampus and hippocampal lesions impair this recall, remote memory retrieval is impaired by cortical lesions, and their recall activates cortical areas (157). The fact that EE restores both new learning and access to remote memories suggests that the effects of EE are probably widespread within hippocampal and cortical areas.

The authors demonstrated that synaptic-related proteins were increased in EE mice, indicating the presence of new dendritic branching and activation of synaptogenesis. This increase was seen in both the hippocampus and the cortex, strengthening the idea that the behavioral effects they reported might be related to these anatomical changes. Prior studies had also shown an effect of EE on neural connectivity, and these results had been taken as an indication that synaptic plasticity was induced. But the authors also went a step further. They first demonstrated that EE increased histone acetylation in the hippocampus and, to a lesser extent, in the cortex of wild-type mice. The effects of EE on wild-type mice suggested that the effects of EE in the p25 transgenic mice might be mediated, at least in part, by histone acetylation. Indeed, the authors also found that promoting histone acetylation by means of administration of histone deacetylation inhibitors to these mice also promoted synaptogenesis and recovery from learning and memory deficits, similar to that seen with exposure to EE, again without affecting the degree of neurodegeneration.

More recently, Graff et al. (179) showed that cognitive capacities in the neurodegenerating brain are constrained by an epigenetic blockade of gene transcription that is potentially reversible. Over the past decade, several studies have reported sporadic cases of reduced histone acetylation in animal models of neurodegeneration that are characterized by cognitive decline, including models of AD (see Ref. 178). Graff et al. (179) investigated whether HDAC2 mediates cognitive deficits associated with neurodegeneration, in CK-p25 mice, the same mice used in the Fischer et al. (146). They found that HDAC2 was significantly increased in neuronal nuclei in hippocampal area CA1 in CK-p25 mice compared with control littermates. Moreover, histone acetylation and expression of genes important for learning and memory were reduced by HDAC2. Counteracting the increase in HDAC2 "unlocks the repression of these genes, reinstates structural and synaptic plasticity, and abolishes neurodegeneration-associated memory impairments" (179).

Some studies have also modeled in animals interventions based only on physical exercise. Spatial learning is enhanced in old mice following voluntary wheel running or treadmill exercise (356; for review, see for instance Refs. 35, 261, 311, 359, 404, 509). Particularly interesting are the papers investigating the effects of exercise initiated in

already aged animals. In Marlatt et al. (311), 9-mo-old C57 female mice were provided with a running wheel or left in standard environment; they were injected with bromodeoxyuridine to label newborn cells. The results show that after 6 mo of running, females had better retention of spatial memory, elevated neurogenesis, and higher mature BDNF peptide levels in the hippocampus. O'Callaghan et al. (359) assessed the effects of 8 mo of treadmill exercise, begun in middle age, on hippocampal LTP and on spatial learning in rats. They found that the exercised group exhibited less age-related decline in LTP and in spatial learning and more NGF and BDNF mRNA in dentate gyrus. Barrientos et al. (35) built on their previous findings that a severe bacterial infection compromises the cognitive status of aged rats more than in younger adult rats. They concluded that the infection produces a neuroinflammatory response and that this response is amplified in the aged brain, possibly due to sensitized microglia in aging, even normal aging. In the 2012 study, Barrientos et al. (35) examined voluntary exercise in very old (24 mo old) rats as a neuroprotective therapeutic in their bacterial infection model. The authors point out that "although aged rats ran only an average of 0.7 km per week, this small amount of exercise was sufficient to completely reverse infection-induced impairments in hippocampus-dependent long-term memory compared with sedentary animals." Interestingly, exercise prevented also the amplified neuroinflammatory response and the reduction in BDNF mRNA observed in the hippocampus of sedentary rats and strongly reduced age-associated microglial sensitization. Finally, Kumar et al. (261) studied the effects of 10–12 wk of exercise condition on aged (20–22 mo) male rats. They found that recognition memory was enhanced in exercised compared with sedentary rats. Exercise reversed age-related changes in hippocampal LTD and LTP, rescuing hippocampal synaptic plasticity. Siette et al. (457) found a highly selective age-related deficit in place recognition memory that is stable across retest sessions and correlates strongly with loss of hippocampal synapses. Twelve weeks of voluntary running at 20 mo of age completely rescued the deficit. In addition, voluntary running restored presynaptic density in the dentate gyrus and CA3 hippocampal subregions in aged rats to levels even beyond those observed in younger animals, in which exercise had no functional or synaptic effects. In contrast, hippocampal neurogenesis increased in both young and aged rats after physical exercise but was not linked with performance in the place recognition task. Analysis based on synaptic covariance patterns to characterize efficient intrahippocampal connectivity revealed that voluntary running completely reverses the profound degradation of hippocampal network efficiency that accompanies sedentary aging. Furthermore, at an individual animal level, both overall hippocampal presynaptic density and subregional connectivity independently contribute to prediction of successful place recognition memory performance. Thus exercise is effective in improving hippocampal synaptic plasticity, hippocampal response to inflammation, hippocampal neurogenesis, and hippocampus-dependent learning not only when initiated in adulthood but also when initiated in middle and even in elderly age. BDNF, which is decreased in the aging hippocampus and is strongly affected by exercise (3, 104) and IGF-I (81), seems central to the exercise effects.

Very similar conclusions can be drawn form the literature on physical exercise effects in aged, already symptomatic, AD animal models. Nichol et al. (353) tested the effect of voluntary wheel-running on memory and hippocampal plasticity in APOE epsilon3 and APOE epsilon4 transgenic mice at 10–12 mo of age. They found that sedentary epsilon4 mice exhibited deficits in spatial memory; 6 wk of wheel-running in epsilon4 mice resulted in improvements of spatial memory to the level of epsilon3 mice. Hippocampal BDNF levels were similar in epsilon3 and epsilon4 mice and, after exercise, the same was true for BDNF. In sedentary epsilon4 mice, hippocampal BDNF TrkB receptors were halved with respect to epsilon3 mice; this difference was abolished by exercise. Parachicova et al. (369) found that running improved cognitive performance of aged Tg2576 mice, a model carrying a human FAD mutation in APP gene, and reduced proinflammatory markers. Garcia-Mesa et al. (166) investigated the effects of running on male and female 3xTg-AD mice at an early pathological stage (4 mo old) or a moderate pathological stage (7 mo old). Cognitive deficits were present in the 3xTg-AD mice along with alteration in synaptic function and LTP impairment in vivo and AD pathology and oxidative-related changes. Exercise treatment ameliorated cognitive deterioration, synaptic changes were partially reduced by exercise, and oxidative stress was diminished.

In conclusion, EE effects on animal models of physiological aging and/or progressive neurodegeneration strongly rely on an enhancement of neural plasticity, since a complete cognitive rescue is frequently achieved with no evidence for a complete rescue of the already existing pathology. In AD models, an action on soluble forms of Aβ must also be taken into account and investigated. Cumulatively, these results show that the factors regulated by EE in ameliorating disease progression in AD models impact AD pathology but are also, more in general, neuroprotective and promote neural plasticity, suggesting that an aged brain, or even a diseased brain, may have potentialities for repair in response to environmental stimulation that we have not yet explored. It has to be underlined that the EE effects in AD models could also be linked to modification of peripheral physiology, which in its turn impact on brain function and plasticity. As an example, EE starting in adulthood modifies immunopro-

files in spleen and thymus (19). Peripheral, blood-borne factors, in addition to IGF-I, could therefore contribute not only to regulate hippocampal neurogenesis and cognitive functions (see Ref. 513) but also to EE and exercise effects on aging and age-related neurodegenerative disease.

V. CONCLUDING REMARKS

One first general remark is on the nature of the EE approach and on its uniqueness and potentialities in the study of brain plasticity. The work reviewed in this paper has shown that EE, a totally noninvasive procedure, has powerful effects on brain plasticity, evident in developing, adult, and even aging brain, under both physiological and pathological conditions. In contrast to other classic experimental paradigms based on deprivation methodologies (e.g., monocular deprivation, whisker removal), EE results in substantial increments in the quality and intensity of experience-dependent stimulation of brain circuits in different modalities. Thus studies on EE ask the brain questions on its neural plasticity processes avoiding the use of experimental pathology and nociceptive stimuli and, therefore, provide to researchers data particularly useful for designing studies aimed at favoring functional abilitation/rehabilitation through optimization of the environmental context.

As discussed in section I, EE is not simply a way of restoring "natural" levels of stimulation in otherwise deprived laboratory animals; indeed, enriching the environment in terms of physical exercise or cognitive and social stimulation has a dramatic impact also on humans. One feature that clearly emerges from the literature reviewed is that different protocols of EE have been used in terms of animal gender, age at EE onset, EE duration, and setting. Despite this source of variance, the general beneficial impact of EE on specific functional domains is not challenged by the results obtained in different laboratories. However, an effort towards the clarification of the effects of systematically varying specific features of EE protocol such as those listed above would undoubtedly facilitate the exchange of results and accelerate the understanding of EE mechanisms of action.

A second necessary remark is on the EE capacity to positively impact on the developing brain, interacting with developmental programs and with the occurrence of critical periods for experience-dependent plasticity. Besides the conceptual significance of this outstanding effect for a basic knowledge of the gene-environment interplay, the possibility to modulate key processes underlying the construction of personality has tremendous consequences in fields like early childhood education. Opposite to the severe and often pathological deficits caused by harsh conditions such as those deriving from living in orphanages characterized by very little attention from caregivers, improving the quality of the external environment in terms of richer opportunities for parental, social, motor, and cognitive stimulation can help the brain to fully wield its potential, with enduring traces in essential domains such as IQ, social disposition, and coping with stress and life challenges. A child's environment is the gymnasium of the future good citizen.

A third consideration is devoted to the profound impact of lifestyle on physiological and pathological aging processes. This has huge economical consequences for the society. In 2012, the direct costs of caring for patients with Alzheimer's disease or other dementias to American society has been estimated in $200 billion, with a projected $1.1 trillion (in today's dollars) by 2050. With the enduring and frustrating absence of efficacious pharmacological compounds capable to arrest the deterioration of cognitive abilities with aging or the progression of dementia in AD, an active life remains one of the very few accepted prescriptions of medicine for a substantial improvement of brain functions in the elderly.

Finally, we would like to emphasize that the great success of the EE approach should not be hailed as a miracle, as it stands on its ability to impact at multiple molecular substrate levels in the brain, including stimulation of maturational processes by enhanced activation of growth factors, reopening of plasticity windows through reduced intracortical inhibition and upregulation of plastic structural and functional changes by neurotrophin increments, which could in turn promote the expression of genes specifically involved in brain plasticity. A few molecular pathways stand out as particularly important mediators of the EE effects on brain plasticity throughout the lifetime, namely, BDNF, IGF-I, GABA, and serotonin; a summary of the effects and mediators of EE is shown in **FIGURE 3**.

Application of paradigms akin to EE can open the way for a new era of endogenous pharmacotherapy, whereby stimulation of key molecular pathways involved in neural plasticity is not necessarily obtained by external administration of active substances, but using the potential of noninvasive strategies of environmental stimulation to enhance the spontaneous reparative potential held by the brain. We strongly believe this paradigm might lead to a new approach to therapy, possibly highly successful for the treatment of several neurological diseases.

VI. CHALLENGES AND OPEN QUESTIONS

Admittedly, more than 50 years of research in the EE field has raised a fair number of questions. Here we provide a tentative list, based on personal, nonexhaustive choices made by the authors.

While the beneficial effects of tactile stimulation in newborns and of physical exercise from youth to elderly are well established, very little is known on the specific role exerted

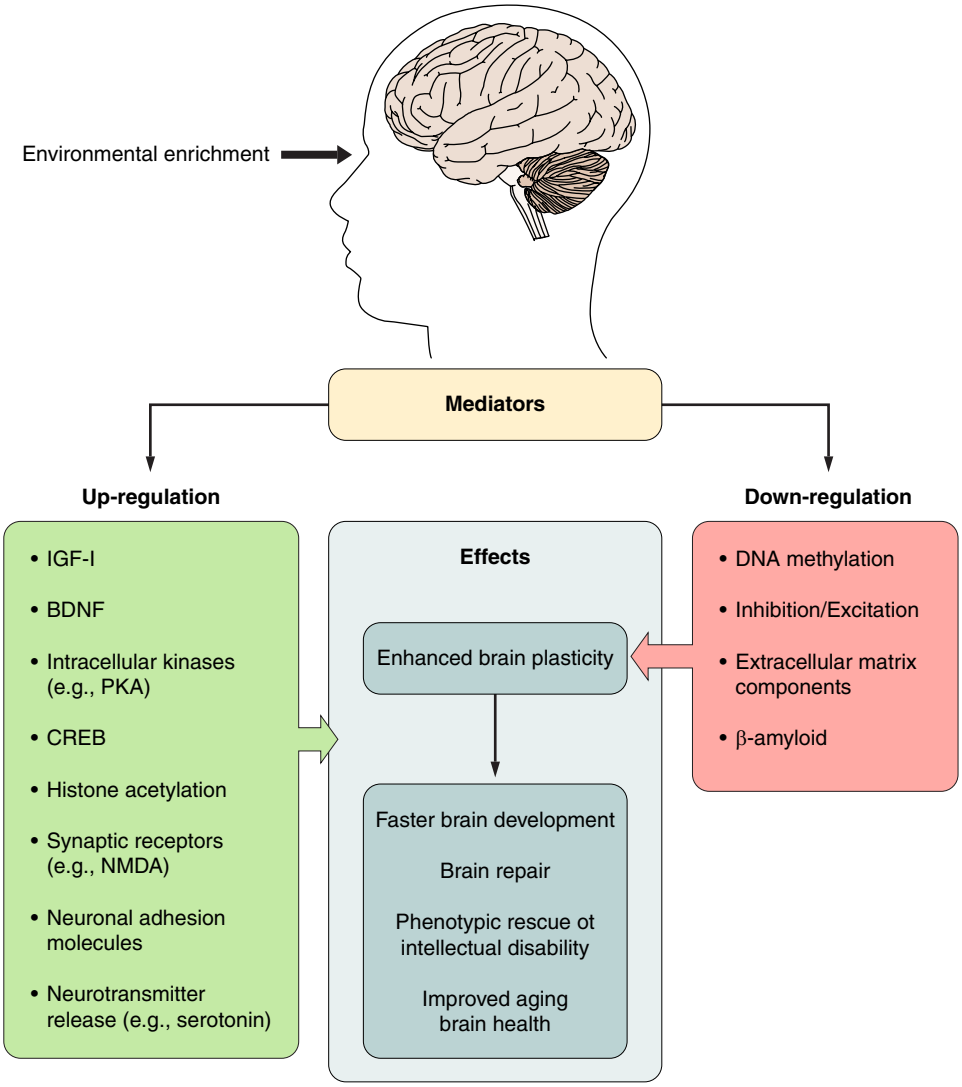

FIGURE 3. Endogenous pharmacotherapy by means of EE paradigms. In parallel with exogenous pharmacologically active substances, exposure to enriched living conditions can be successfully used to enhance neural plasticity and functional compensation, promoting brain development, learning, and memory functions and facilitating brain repair processes. These effects are elicited by a number of well-established key molecular factors, acting at the single neuron and neural network level. We have divided the factors through which EE enhances brain plasticity into those that are upregulated and those that are downregulated. For simplicity, we have not listed actions of EE on factors whose involvement in brain plasticity is still under investigation (e.g., neuroinflammation or angiogenesis).

by cognitive stimulation interventions, both in animal models and in humans. To what extent can engaging in challenging mental activities contribute to the entire EE experience effects?

What are the effects of EE on neural systems that regulate the arousal state? Is the average amount and structure of sleep modified by living in stimulating environmental conditions?

What is the relationship between exposure to EE and control of feeding behavior? To what extent do the beneficial EE effects depend on a regulation of fine metabolic processes?

Recent research has shown that blood-brain barriers located at brain vessels and choroids plexuses and regulating passage of blood components into the brain parenchyma and cerebrospinal fluid are not impermeable for serum proteins, but can instead exhibit localized transport of circulating hormones and growth factors through neuronal activity-dependent processes. Which is the impact of environment in this essential pathway for regulation of brain physiology? Can EE be used as a way to temporarily modify blood-brain barrier selectivity to facilitate entrance of key pharmacologically active compounds?

A very challenging question is related to the molecular mechanisms underlying the beneficial effects elicited, on

cerebral plasticity, by exposure to enriched environmental conditions. Which factors are more amenable of being artificially manipulated to mimic or to strengthen the impact of EE?

ACKNOWLEDGMENTS

A. Sale and N. Berardi contributed equally to this work.

Address for reprint requests and other correspondence: A. Sale, Institute of Neuroscience CNR, Via Moruzzi 1, 56124 Pisa, Italy (e-mail: sale@in.cnr.it).

GRANTS

This work was supported by a grant from "Fondazione Pisa" (to L. Maffei).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES

1. Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, Petrovitch H. Walking and dementia in physically capable elderly men. *JAMA* 292: 1447–1453, 2004.

2. ACOG committee. Exercise during pregnancy and the postpartum period. *Int J Gynaecol Obstet* 77: 79–81, 2002.

3. Adlard PA, Perreau VM, Pop V, Cotman CW. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. *J Neurosci* 25: 4217–4221, 2005.

4. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. *Mayo Clin Proc* 86: 876–884, 2011.

5. Aimone JB, Deng W, Gage FH. Adult neurogenesis: integrating theories and separating functions. *Trends Cogn Sci* 14: 325–337, 2010.

6. Aimone JB, Deng W, Gage FH. Resolving new memories: a critical look at the dentate gyrus, adult neurogenesis, and pattern separation. *Neuron* 70: 589–596, 2011.

7. Aimone JB, Wiles J, Gage FH. Potential role for adult neurogenesis in the encoding of time in new memories. *Nat Neurosci* 9: 723–727, 2006.

8. Alarcon JM, Malleret G, Touzani K, Vronskaya S, Ishii S, Kandel ER, Barco A. Chromatin acetylation, memory, and LTP are impaired in CBP+/− mice: a model for the cognitive deficit in Rubinstein-Taybi syndrome and its amelioration. *Neuron* 42: 947–959, 2004.

9. Alexander GE, Furey ML, Grady CL, Pietrini P, Brady DR, Mentis MJ, Schapiro MB. Association of premorbid intellectual function with cerebral metabolism in Alzheimer's disease: implications for the cognitive reserve hypothesis. *Am J Psychiatry* 154: 165–172, 1997.

10. Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat Genet* 23: 185–188, 1999.

11. Amrein I, Isler K, Lipp HP. Comparing adult hippocampal neurogenesis in mammalian species and orders: influence of chronological age and life history stage. *Eur J Neurosci* 34: 978–987, 2011.

12. Amrein I, Slomianka L. A morphologically distinct granule cell type in the dentate gyrus of the red fox correlates with adult hippocampal neurogenesis. *Brain Res* 1328: 12–24, 2010.

13. Angevaren M, Aufdemkampe G, Verhaar HJ, Aleman A, Vanhees L. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev* CD005381, 2008.

14. Angevaren M, Aufdemkampe G, Verhaar HJ, Aleman A, Vanhees L. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev* CD005381, 2008.

15. Anggono V, Clem RL, Huganir RL. PICK1 loss of function occludes homeostatic synaptic scaling. *J Neurosci* 31: 2188–2196, 2011.

16. Apostolova LG, Green AE, Babakchanian S, Hwang KS, Chou YY, Toga AW, Thompson PM. Hippocampal atrophy and ventricular enlargement in normal aging, mild cognitive impairment (MCI), and Alzheimer Disease. *Alzheimer Dis Assoc Disord* 26: 17–27, 2012.

17. Arendash GW, Garcia MF, Costa DA, Cracchiolo JR, Wefes IM, Potter H. Environmental enrichment improves cognition in aged Alzheimer's transgenic mice despite stable beta-amyloid deposition. *Neuroreport* 15: 1751–1754, 2004.

18. Argandona EG, Bengoetxea H, Ortuzar N, Bulnes S, Rico-Barrio I, Lafuente JV. Vascular endothelial growth factor: adaptive changes in the neuroglialvascular unit. *Curr Neurovasc Res* 9: 72–81, 2012.

19. Arranz L, De Castro NM, Baeza I, Gimenez-Llort L, De la Fuente M. Effect of environmental enrichment on the immunoendocrine aging of male and female triple-transgenic 3xTg-AD mice for Alzheimer's disease. *J Alzheimers Dis* 25: 727–737.

20. Artola A, von Frijtag JC, Fermont PC, Gispen WH, Schrama LH, Kamal A, Spruijt BM. Long-lasting modulation of the induction of LTD and LTP in rat hippocampal CA1 by behavioural stress and environmental enrichment. *Eur J Neurosci* 23: 261–272, 2006.

21. Asaka Y, Jugloff DG, Zhang L, Eubanks JH, Fitzsimonds RM. Hippocampal synaptic plasticity is impaired in the Mecp2-null mouse model of Rett syndrome. *Neurobiol Dis* 21: 217–227, 2006.

22. Astle AT, Webb BS, McGraw PV. Can perceptual learning be used to treat amblyopia beyond the critical period of visual development? *Ophthalmic Physiol Opt* 31: 564–573, 2011.

23. Baker LD, Bayer-Carter JL, Skinner J, Montine TJ, Cholerton BA, Callaghan M, Leverenz JB, Walter BK, Tsai E, Postupna N, Lampe J, Craft S. High-intensity physical activity modulates diet effects on cerebrospinal amyloid-beta levels in normal aging and mild cognitive impairment. *J Alzheimers Dis* 28: 137–146, 2012.

24. Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A, Plymate SR, Fishel MA, Watson GS, Cholerton BA, Duncan GE, Mehta PD, Craft S. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Arch Neurol* 67: 71–79, 2010.

25. Baranes D, Lederfein D, Huang YY, Chen M, Bailey CH, Kandel ER. Tissue plasminogen activator contributes to the late phase of LTP and to synaptic growth in the hippocampal mossy fiber pathway. *Neuron* 21: 813–825, 1998.

26. Barnes CA. Secrets of aging: What does a normally aging brain look like? *F1000 Biol Rep* 3: 22, 2011.

27. Baro JA, Lehmkuhle S, Kratz KE. Electroretinograms and visual evoked potentials in long-term monocularly deprived cats. *Invest Ophthalmol Vis Sci* 31: 1405–1409, 1990.

28. Baroncelli L, Bonaccorsi J, Milanese M, Bonifacino T, Giribaldi F, Manno I, Cenni MC, Berardi N, Bonanno G, Maffei L, Sale A. Enriched experience and recovery from amblyopia in adult rats: impact of motor, social and sensory components. *Neuropharmacology* 62: 2388–2397, 2012.

29. Baroncelli L, Braschi C, Maffei L. Visual depth perception in normal and deprived rats: effects of environmental enrichment. *Neuroscience* 236: 313–319, 2013.

30. Baroncelli L, Braschi C, Spolidoro M, Begenisic T, Maffei L, Sale A. Brain plasticity and disease: a matter of inhibition. *Neural Plast* 2011: 286073, 2011.

31. Baroncelli L, Maffei L, Sale A. New perspectives in amblyopia therapy on adults: a critical role for the excitatory/inhibitory balance. *Front Cell Neurosci* 5: 25, 2011.

32. Baroncelli L, Sale A, Viegi A, Maya Vetencourt JF, De Pasquale R, Baldini S, Maffei L. Experience-dependent reactivation of ocular dominance plasticity in the adult visual cortex. *Exp Neurol* 226: 100–109, 2010.

33. Baroncelli L, Sale A, Viegi A, Maya Vetencourt JF, De Pasquale R, Baldini S, Maffei L. Experience-dependent reactivation of ocular dominance plasticity in the adult visual cortex. *Exp Neurol* 226: 100–109.

34. Barr CS, Newman TK, Shannon C, Parker C, Dvoskin RL, Becker ML, Schwandt M, Champoux M, Lesch KP, Goldman D, Suomi SJ, Higley JD. Rearing condition and rh5-HTTLPR interact to influence limbic-hypothalamic-pituitary-adrenal axis response to stress in infant macaques. *Biol Psychiatry* 55: 733–738, 2004.

35. Barrientos RM, Frank MG, Crysdale NY, Chapman TR, Ahrendsen JT, Day HE, Campeau S, Watkins LR, Patterson SL, Maier SF. Little exercise, big effects: reversing aging and infection-induced memory deficits, and underlying processes. *J Neurosci* 31: 11578–11586, 2011.

36. Bartoletti A, Medini P, Berardi N, Maffei L. Environmental enrichment prevents effects of dark-rearing in the rat visual cortex. *Nat Neurosci* 7: 215–216, 2004.

37. Bavelier D, Levi DM, Li RW, Dan Y, Hensch TK. Removing brakes on adult brain plasticity: from molecular to behavioral interventions. *J Neurosci* 30: 14964–14971, 2010.

38. Bavelier D, Neville HJ. Cross-modal plasticity: where and how? *Nat Rev Neurosci* 3: 443–452, 2002.

39. Bear MF, Singer W. Modulation of visual cortical plasticity by acetylcholine and noradrenaline. *Nature* 320: 172–176, 1986.

40. Beaulieu C, Cynader M. Effect of the richness of the environment on neurons in cat visual cortex. I. Receptive field properties. *Brain Res* 53: 71–81, 1990.

41. Beaulieu C, Cynader M. Effect of the richness of the environment on neurons in cat visual cortex. II. Spatial and temporal frequency characteristics. *Brain Res* 53: 82–88, 1990.

42. Begenisic T, Spolidoro M, Braschi C, Baroncelli L, Milanese M, Pietra G, Fabbri ME, Bonanno G, Cioni G, Maffei L, Sale A. Environmental enrichment decreases GABAergic inhibition and improves cognitive abilities, synaptic plasticity, and visual functions in a mouse model of Down syndrome. *Front Cell Neurosci* 5: 29, 2011.

43. Belichenko PV, Kleschevnikov AM, Masliah E, Wu C, Takimoto-Kimura R, Salehi A, Mobley WC. Excitatory-inhibitory relationship in the fascia dentata in the Ts65Dn mouse model of Down syndrome. *J Comp Neurol* 512: 453–466, 2009.

44. Belz EE, Kennell JS, Czambel RK, Rubin RT, Rhodes ME. Environmental enrichment lowers stress-responsive hormones in singly housed male and female rats. *Pharmacol Biochem Behav* 76: 481–486, 2003.

45. Benaroya-Milshtein N, Hollander N, Apter A, Kukulansky T, Raz N, Wilf A, Yaniv I, Pick CG. Environmental enrichment in mice decreases anxiety, attenuates stress responses and enhances natural killer cell activity. *Eur J Neurosci* 20: 1341–1347, 2004.

46. Benesova O, Pavlik A. Perinatal treatment with glucocorticoids and the risk of maldevelopment of the brain. *Neuropharmacology* 28: 89–97, 1989.

47. Bennett JC, McRae PA, Levy LJ, Frick KM. Long-term continuous, but not daily, environmental enrichment reduces spatial memory decline in aged male mice. *Neurobiol Learn Mem* 85: 139–152, 2006.

48. Berardi N, Braschi C, Capsoni S, Cattaneo A, Maffei L. Environmental enrichment delays the onset of memory deficits and reduces neuropathological hallmarks in a mouse model of Alzheimer-like neurodegeneration. *J Alzheimers Dis* 11: 359–370, 2007.

49. Berardi N, Maffei L. From visual experience to visual function: roles of neurotrophins. *J Neurobiol* 41: 119–126, 1999.

50. Berardi N, Pizzorusso T, Maffei L. Critical periods during sensory development. *Curr Opin Neurobiol* 10: 138–145, 2000.

51. Berardi N, Pizzorusso T, Ratto GM, Maffei L. Molecular basis of plasticity in the visual cortex. *Trends Neurosci* 26: 369–378, 2003.

52. Berchtold NC, Cribbs DH, Coleman PD, Rogers J, Head E, Kim R, Beach T, Miller C, Troncoso J, Trojanowski JQ, Zielke HR, Cotman CW. Gene expression changes in the course of normal brain aging are sexually dimorphic. *Proc Natl Acad Sci USA* 105: 15605–15610, 2008.

53. Bernstein L. A study of some enriching variables in a free-environment for rats. *J Psychosom Res* 17: 85–88, 1973.

54. Berridge CW, Waterhouse BD. The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Res* 42: 33–84, 2003.

55. Bi GQ, Poo MM. Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. *J Neurosci* 18: 10464–10472, 1998.

56. Bick-Sander A, Steiner B, Wolf SA, Babu H, Kempermann G. Running in pregnancy transiently increases postnatal hippocampal neurogenesis in the offspring. *Proc Natl Acad Sci USA* 103: 3852–3857, 2006.

57. Bickerdike MJ, Wright IK, Marsden CA. Social isolation attenuates rat forebrain 5-HT release induced by KCl stimulation and exposure to a novel environment. *Behav Pharmacol* 4: 231–236, 1993.

58. Black JE, Isaacs KR, Anderson BJ, Alcantara AA, Greenough WT. Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. *Proc Natl Acad Sci USA* 87: 5568–5572, 1990.

59. Bliss TV, Cooke SF. Long-term potentiation and long-term depression: a clinical perspective. *Clinics* 66 Suppl 1: 3–17, 2011.

60. Blue ME, Naidu S, Johnston MV. Altered development of glutamate and GABA receptors in the basal ganglia of girls with Rett syndrome. *Exp Neurol* 156: 345–352, 1999.

61. Blurton-Jones M, Kitazawa M, Martinez-Coria H, Castello NA, Muller FJ, Loring JF, Yamasaki TR, Poon WW, Green KN, LaFerla FM. Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. *Proc Natl Acad Sci USA* 106: 13594–13599, 2009.

62. Bonhoeffer T. Neurotrophins and activity-dependent development of the neocortex. *Curr Opin Neurobiol* 6: 119–126, 1996.

63. Bourgeon S, Xerri C, Coq JO. Abilities in tactile discrimination of textures in adult rats exposed to enriched or impoverished environments. *Behav Brain Res* 153: 217–231, 2004.

64. Bradley KM, O'Sullivan VT, Soper ND, Nagy Z, King EM, Smith AD, Shepstone BJ. Cerebral perfusion SPET correlated with Braak pathological stage in Alzheimer's disease. *Brain* 125: 1772–1781, 2002.

65. Branchi I, D'Andrea I, Cirulli F, Lipp HP, Alleva E. Shaping brain development: mouse communal nesting blunts adult neuroendocrine and behavioral response to social stress and modifies chronic antidepressant treatment outcome. *Psychoneuroendocrinology* 35: 743–751, 2010.

66. Branchi I, D'Andrea I, Sietzema J, Fiore M, Di Fausto V, Aloe L, Alleva E. Early social enrichment augments adult hippocampal BDNF levels and survival of BrdU-positive cells while increasing anxiety- and "depression"-like behavior. *J Neurosci Res* 83: 965–973, 2006.

67. Brenes JC, Rodriguez O, Fornaguera J. Differential effect of environment enrichment and social isolation on depressive-like behavior, spontaneous activity and serotonin and norepinephrine concentration in prefrontal cortex and ventral striatum. *Pharmacol Biochem Behav* 89: 85–93, 2008.

68. Brown J, Cooper-Kuhn CM, Kempermann G, Van Praag H, Winkler J, Gage FH, Kuhn HG. Enriched environment and physical activity stimulate hippocampal but not olfactory bulb neurogenesis. *Eur J Neurosci* 17: 2042–2046, 2003.

69. Buchman AS, Boyle PA, Yu L, Shah RC, Wilson RS, Bennett DA. Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology* 78: 1323–1329, 2012.

70. Bugg JM, Head D. Exercise moderates age-related atrophy of the medial temporal lobe. *Neurobiol Aging* 32: 506–514, 2011.

71. Burke SN, Barnes CA. Neural plasticity in the ageing brain. *Nat Rev Neurosci* 7: 30–40, 2006.

72. Cabeza R, Anderson ND, Locantore JK, McIntosh AR. Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage* 17: 1394–1402, 2002.

73. Cai R, Guo F, Zhang J, Xu J, Cui Y, Sun X. Environmental enrichment improves behavioral performance and auditory spatial representation of primary auditory cortical neurons in rat. *Neurobiol Learn Mem* 91: 366–376, 2009.

74. Caldji C, Tannenbaum B, Sharma S, Francis D, Plotsky PM, Meaney MJ. Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat. *Proc Natl Acad Sci USA* 95: 5335–5340, 1998.

75. Campeau S, Nyhuis TJ, Sasse SK, Kryskow EM, Herlihy L, Masini CV, Babb JA, Greenwood BN, Fleshner M, Day HE. Hypothalamic pituitary adrenal axis responses to low-intensity stressors are reduced after voluntary wheel running in rats. *J Neuroendocrinol* 22: 872–888, 2010.

76. Cancedda L, Putignano E, Sale A, Viegi A, Berardi N, Maffei L. Acceleration of visual system development by environmental enrichment. *J Neurosci* 24: 4840–4848, 2004.

77. Carlson MC, Helms MJ, Steffens DC, Burke JR, Potter GG, Plassman BL. Midlife activity predicts risk of dementia in older male twin pairs. *Alzheimers Dement* 4: 324–331, 2008.

78. Carro E, Nunez A, Busiguina S, Torres-Aleman I. Circulating insulin-like growth factor I mediates effects of exercise on the brain. *J Neurosci* 20: 2926–2933, 2000.

79. Carro E, Trejo JL, Busiguina S, Torres-Aleman I. Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. *J Neurosci* 21: 5678–5684, 2001.

80. Carro E, Trejo JL, Gomez-Isla T, LeRoith D, Torres-Aleman I. Serum insulin-like growth factor I regulates brain amyloid-beta levels. *Nat Med* 8: 1390–1397, 2002.

81. Caspi A, Moffitt TE. Gene-environment interactions in psychiatry: joining forces with neuroscience. *Nat Rev Neurosci* 7: 583–590, 2006.

82. Catlow BJ, Rowe AR, Clearwater CR, Mamcarz M, Arendash GW, Sanchez-Ramos J. Effects of environmental enrichment and physical activity on neurogenesis in transgenic PS1/APP mice. *Brain Res* 1256: 173–179, 2009.

83. Caviness VS Jr. Time of neuron origin in the hippocampus and dentate gyrus of normal and reeler mutant mice: an autoradiographic analysis. *J Comp Neurol* 151: 113–120, 1973.

84. Chae CH, Jung SL, An SH, Park BY, Wang SW, Cho IH, Cho JY, Kim HT. Treadmill exercise improves cognitive function and facilitates nerve growth factor signaling by activating mitogen-activated protein kinase/extracellular signal-regulated kinase1/2 in the streptozotocin-induced diabetic rat hippocampus. *Neuroscience* 164: 1665–1673, 2009.

85. Chahrour M, Jung SY, Shaw C, Zhou X, Wong ST, Qin J, Zoghbi HY. MeCP2, a key contributor to neurological disease, activates and represses transcription. *Science* 320: 1224–1229, 2008.

86. Chakrabarti L, Scafidi J, Gallo V, Haydar TF. Environmental enrichment rescues postnatal neurogenesis defect in the male and female Ts65Dn mouse model of Down syndrome. *Dev Neurosci* 33: 428–441, 2011.

87. Champagne FA, Francis DD, Mar A, Meaney MJ. Variations in maternal care in the rat as a mediating influence for the effects of environment on development. *Physiol Behav* 79: 359–371, 2003.

88. Champagne FA, Weaver IC, Diorio J, Dymov S, Szyf M, Meaney MJ. Maternal care associated with methylation of the estrogen receptor-alpha1b promoter and estrogen receptor-alpha expression in the medial preoptic area of female offspring. *Endocrinology* 147: 2909–2915, 2006.

89. Chang YM, Rosene DL, Killiany RJ, Mangiamele LA, Luebke JI. Increased action potential firing rates of layer 2/3 pyramidal cells in the prefrontal cortex are significantly related to cognitive performance in aged monkeys. *Cereb Cortex* 15: 409–418, 2005.

90. Chapillon P, Manneche C, Belzung C, Caston J. Rearing environmental enrichment in two inbred strains of mice. 1. Effects on emotional reactivity. *Behav Genet* 29: 41–46, 1999.

91. Charil A, Laplante DP, Vaillancourt C, King S. Prenatal stress and brain development. *Brain Res Rev* 65: 56–79, 2010.

92. Chen JL, Lin WC, Cha JW, So PT, Kubota Y, Nedivi E. Structural basis for the role of inhibition in facilitating adult brain plasticity. *Nature Neurosci* 14: 587–594, 2011.

94. Chen WG, Chang Q, Lin Y, Meissner A, West AE, Griffith EC, Jaenisch R, Greenberg ME. Derepression of BDNF transcription involves calcium-dependent phosphorylation of MeCP2. *Science* 302: 885–889, 2003.

95. Churchill JD, Galvez R, Colcombe S, Swain RA, Kramer AF, Greenough WT. Exercise, experience and the aging brain. *Neurobiol Aging* 23: 941–955, 2002.

96. Ciucci F, Putignano E, Baroncelli L, Landi S, Berardi N, Maffei L. Insulin-like growth factor 1 (IGF-1) mediates the effects of enriched environment (EE) on visual cortical development. *PLoS One* 2: e475, 2007.

97. Clapp JF 3rd, Simonian S, Lopez B, Appleby-Wineberg S, Harcar-Sevcik R. The one-year morphometric and neurodevelopmental outcome of the offspring of women who continued to exercise regularly throughout pregnancy. *Am J Obstet Gynecol* 178: 594–599, 1998.

98. Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, Webb A, Jerome GJ, Marquez DX, Elavsky S. Cardiovascular fitness, cortical plasticity, aging. *Proc Natl Acad Sci USA* 101: 3316–3321, 2004.

99. Collingridge GL, Peineau S, Howland JG, Wang YT. Long-term depression in the CNS. *Nat Rev Neurosci* 11: 459–473, 2010.

101. Cooke SF, Bear MF. Visual experience induces long-term potentiation in the primary visual cortex. *J Neurosci* 30: 16304–16313, 2010.

102. Coq JO, Xerri C. Environmental enrichment alters organizational features of the forepaw representation in the primary somatosensory cortex of adult rats. *Exp Brain Res* 121: 191–204, 1998.

103. Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci* 25: 295–301, 2002.

104. Covington HE, 3rd Maze I, Sun H, Bomze HM, DeMaio KD, Wu EY, Dietz DM, Lobo MK, Ghose S, Mouzon E, Neve RL, Tamminga CA, Nestler EJ. A role for repressive histone methylation in cocaine-induced vulnerability to stress. *Neuron* 71: 656–670, 2011.

105. Cruz JC, Tsai LH. Cdk5 deregulation in the pathogenesis of Alzheimer's disease. *Trends Mol Med* 10: 452–458, 2004.

106. Curley JP, Davidson S, Bateson P, Champagne FA. Social enrichment during postnatal development induces transgenerational effects on emotional and reproductive behavior in mice. *Front Behav Neurosci* 3: 25, 2009.

107. D'Alessio AC, Szyf M. Epigenetic tete-a-tete: the bilateral relationship between chromatin modifications and DNA methylation. *Biochem Cell Biol* 84: 463–476, 2006.

108. D'Hooge R, De Deyn PP. Applications of the Morris water maze in the study of learning and memory. *Brain Res* 36: 60–90, 2001.

109. Dani VS, Chang Q, Maffei A, Turrigiano GG, Jaenisch R, Nelson SB. Reduced cortical activity due to a shift in the balance between excitation and inhibition in a mouse model of Rett syndrome. *Proc Natl Acad Sci USA* 102: 12560–12565, 2005.

110. Davisson MT, Schmidt C, Akeson EC. Segmental trisomy of murine chromosome 16: a new model system for studying Down syndrome. *Prog Clin Biol Res* 360: 263–280, 1990.

111. Day-Wilson KM, Jones DN, Southam E, Cilia J, Totterdell S. Medial prefrontal cortex volume loss in rats with isolation rearing-induced deficits in prepulse inhibition of acoustic startle. *Neuroscience* 141: 1113–1121, 2006.

112. De Rosa R, Garcia AA, Braschi C, Capsoni S, Maffei L, Berardi N, Cattaneo A. Intranasal administration of nerve growth factor (NGF) rescues recognition memory deficits in AD11 anti-NGF transgenic mice. *Proc Natl Acad Sci USA* 102: 3811–3816, 2005.

113. DeCarli C, Frisoni GB, Clark CM, Harvey D, Grundman M, Petersen RC, Thal LJ, Jin S, Jack CR Jr, Scheltens P. Qualitative estimates of medial temporal atrophy as a predictor of progression from mild cognitive impairment to dementia. *Arch Neurol* 64: 108–115, 2007.

114. Deisseroth K, Bito H, Schulman H, Tsien RW. Synaptic plasticity: a molecular mechanism for metaplasticity. *Curr Biol* 5: 1334–1338, 1995.

115. Desai NS, Cudmore RH, Nelson SB, Turrigiano GG. Critical periods for experience-dependent synaptic scaling in visual cortex. *Nat Neurosci* 5: 783–789, 2002.

116. Devonshire IM, Dommett EJ, Grandy TH, Halliday AC, Greenfield SA. Environmental enrichment differentially modifies specific components of sensory-evoked activity in rat barrel cortex as revealed by simultaneous electrophysiological recordings and optical imaging in vivo. *Neuroscience* 170: 662–669, 2010.

117. Di Garbo A, Mainardi M, Chillemi S, Maffei L, Caleo M. Environmental enrichment modulates cortico-cortical interactions in the mouse. *PLoS One* 6: e25285, 2011.

118. Diamond MC. Response of the brain to enrichment. *An Acad Bras Cienc* 73: 211–220, 2001.

119. Diamond MC, Krech D, Rosenzweig MR. The effects of an enriched environment on the histology of the rat cerebral cortex. *J Comp Neurol* 123: 111–120, 1964.

120. Diamond MC, Law F, Rhodes H, Lindner B, Rosenzweig MR, Krech D, Bennett EL. Increases in cortical depth and glia numbers in rats subjected to enriched environment. *J Comp Neurol* 128: 117–126, 1966.

121. Dierssen M, Benavides-Piccione R, Martinez-Cue C, Estivill X, Florez J, Elston GN, DeFelipe J. Alterations of neocortical pyramidal cell phenotype in the Ts65Dn mouse model of Down syndrome: effects of environmental enrichment. *Cereb Cortex* 13: 758–764, 2003.

122. Diniz DG, Foro CA, Rego CM, Gloria DA, de Oliveira FR, Paes JM, de Sousa AA, Tokuhashi TP, Trindade LS, Turiel MC, Vasconcelos EG, Torres JB, Cunnigham C, Perry VH, Vasconcelos PF, Diniz CW. Environmental impoverishment and aging alter object recognition, spatial learning, and dentate gyrus astrocytes. *Eur J Neurosci* 32: 509–519, 2010.

123. Dityatev A, Schachner M, Sonderegger P. The dual role of the extracellular matrix in synaptic plasticity and homeostasis. *Nat Rev Neurosci* 11: 735–746, 2010.

124. Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A. Neuroplasticity: changes in grey matter induced by training. *Nature* 427: 311–312, 2004.

125. Dudek SM, Bear MF. Homosynaptic long-term depression in area CA1 of hippocampus and effects of *N*-methyl-D-aspartate receptor blockade. *Proc Natl Acad Sci USA* 89: 4363–4367, 1992.

126. Duffy SN, Craddock KJ, Abel T, Nguyen PV. Environmental enrichment modifies the PKA-dependence of hippocampal LTP and improves hippocampus-dependent memory. *Learn Mem* 8: 26–34, 2001.

127. Dupret D, Fabre A, Dobrossy MD, Panatier A, Rodriguez JJ, Lamarque S, Lemaire V, Oliet SH, Piazza PV, Abrous DN. Spatial learning depends on both the addition and removal of new hippocampal neurons. *PLoS Biol* 5: e214, 2007.

128. Durand S, Patrizi A, Quast KB, Hachigian L, Pavlyuk R, Saxena A, Carninci P, Hensch TK, Fagiolini M. NMDA receptor regulation prevents regression of visual cortical function in the absence of Mecp2. *Neuron* 76: 1078–1090, 2012.

129. Engineer ND, Percaccio CR, Pandya PK, Moucha R, Rathbun DL, Kilgard MP. Environmental enrichment improves response strength, threshold, selectivity, and latency of auditory cortex neurons. *J Neurophysiol* 92: 73–82, 2004.

130. Erickson CA, Barnes CA. The neurobiology of memory changes in normal aging. *Exp Gerontol* 38: 61–69, 2003.

131. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H, White SM, Wojcicki TR, Mailey E, Vieira VJ, Martin SA, Pence BD, Woods JA, McAuley E, Kramer AF. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci USA* 108: 3017–3022, 2011.

132. Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH. Neurogenesis in the adult human hippocampus. *Nat Med* 4: 1313–1317, 1998.

133. Escorihuela RM, Fernandez-Teruel A, Tobena A, Vivas NM, Marmol F, Badia A, Dierssen M. Early environmental stimulation produces long-lasting changes on beta-adrenoceptor transduction system. *Neurobiol Learn Mem* 64: 49–57, 1995.

134. Etgen T, Sander D, Huntgeburth U, Poppert H, Forstl H, Bickel H. Physical activity and incident cognitive impairment in elderly persons: the INVADE study. *Arch Intern Med* 170: 186–193, 2010.

135. Fabel K, Wolf SA, Ehninger D, Babu H, Leal-Galicia P, Kempermann G. Additive effects of physical exercise and environmental enrichment on adult hippocampal neurogenesis in mice. *Front Neurosci* 3: 50, 2009.

136. Fabricius K, Helboe L, Steiniger-Brach B, Fink-Jensen A, Pakkenberg B. Stereological brain volume changes in post-weaned socially isolated rats. *Brain Res* 1345: 233–239, 2010.

137. Fagiolini M, Jensen CL, Champagne FA. Epigenetic influences on brain development and plasticity. *Curr Opin Neurobiol* 19: 207–212, 2009.

138. Fagiolini M, Pizzorusso T, Berardi N, Domenici L, Maffei L. Functional postnatal development of the rat primary visual cortex and the role of visual experience: dark rearing and monocular deprivation. *Vision Res* 34: 709–720, 1994.

139. Falkenberg T, Mohammed AK, Henriksson B, Persson H, Winblad B, Lindefors N. Increased expression of brain-derived neurotrophic factor mRNA in rat hippocampus is associated with improved spatial memory and enriched environment. *Neurosci Lett* 138: 153–156, 1992.

140. Farmer J, Zhao X, van Praag H, Wodtke K, Gage FH, Christie BR. Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. *Neuroscience* 124: 71–79, 2004.

141. Feng X, Wang L, Yang S, Qin D, Wang J, Li C, Lv L, Ma Y, Hu X. Maternal separation produces lasting changes in cortisol and behavior in rhesus monkeys. *Proc Natl Acad Sci USA* 108: 14312–14317, 2011.

142. Fernandez F, Garner CC. Over-inhibition: a model for developmental intellectual disability. *Trends Neurosci* 30: 497–503, 2007.

143. Fernandez F, Morishita W, Zuniga E, Nguyen J, Blank M, Malenka RC, Garner CC. Pharmacotherapy for cognitive impairment in a mouse model of Down syndrome. *Nat Neurosci* 10: 411–413, 2007.

144. Fine I, Wade AR, Brewer AA, May MG, Goodman DF, Boynton GM, Wandell BA, MacLeod DI. Long-term deprivation affects visual perception and cortex. *Nat Neurosci* 6: 915–916, 2003.

145. Fischer A, Sananbenesi F, Pang PT, Lu B, Tsai LH. Opposing roles of transient and prolonged expression of p25 in synaptic plasticity and hippocampus-dependent memory. *Neuron* 48: 825–838, 2005.

146. Fischer A, Sananbenesi F, Wang X, Dobbin M, Tsai LH. Recovery of learning and memory is associated with chromatin remodelling. *Nature* 447: 178–182, 2007.

147. Fish EW, Shahrokh D, Bagot R, Caldji C, Bredy T, Szyf M, Meaney MJ. Epigenetic programming of stress responses through variations in maternal care. *Ann NY Acad Sci* 1036: 167–180, 2004.

148. Fleming AS, Kraemer GW, Gonzalez A, Lovic V, Rees S, Melo A. Mothering begets mothering: the transmission of behavior and its neurobiology across generations. *Pharmacol Biochem Behav* 73: 61–75, 2002.

149. Fleming AS, O'Day DH, Kraemer GW. Neurobiology of mother-infant interactions: experience and central nervous system plasticity across development and generations. *Neurosci Biobehav Rev* 23: 673–685, 1999.

150. Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N, Larbig W, Taub E. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature* 375: 482–484, 1995.

151. Fordyce DE, Farrar RP. Enhancement of spatial learning in F344 rats by physical activity and related learning-associated alterations in hippocampal and cortical cholinergic functioning. *Behav Brain Res* 46: 123–133, 1991.

152. Foster TC, Gagne J, Massicotte G. Mechanism of altered synaptic strength due to experience: relation to long-term potentiation. *Brain Res* 736: 243–250, 1996.

153. Fowden AL. The insulin-like growth factors and feto-placental growth. *Placenta* 24: 803–812, 2003.

154. Fox SE, Levitt P, Nelson CA 3rd. How the timing and quality of early experiences influence the development of brain architecture. *Child Dev* 81: 28–40, 2010.

155. Francis DD, Diorio J, Plotsky PM, Meaney MJ. Environmental enrichment reverses the effects of maternal separation on stress reactivity. *J Neurosci* 22: 7840–7843, 2002.

156. Francis DD, Meaney MJ. Maternal care and the development of stress responses. *Curr Opin Neurobiol* 9: 128–134, 1999.

157. Frankland PW, Bontempi B. The organization of recent and remote memories. *Nat Rev Neurosci* 6: 119–130, 2005.

158. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. *Lancet Neurol* 3: 343–353, 2004.

159. Fratiglioni L, Wang HX. Brain reserve hypothesis in dementia. *J Alzheimers Dis* 12: 11–22, 2007.

160. Frenkel MY, Bear MF. How monocular deprivation shifts ocular dominance in visual cortex of young mice. *Neuron* 44: 917–923, 2004.

161. Freret T, Billard JM, Schumann-Bard P, Dutar P, Dauphin F, Boulouard M, Bouet V. Rescue of cognitive aging by long-lasting environmental enrichment exposure initiated before median lifespan. *Neurobiol Aging* 33: 1005 e1001–1010, 2012.

162. Frisoni GB, Padovani A, Wahlund LO. The predementia diagnosis of Alzheimer disease. *Alzheimer Dis Assoc Disord* 18: 51–53, 2004.

163. Frodl T, O'Keane V. How does the brain deal with cumulative stress? *A* review with focus on developmental stress, HPA axis function and hippocampal structure in humans. *Neurobiol Dis* 52: 24–37, 2013.

164. Frye CA, Orecki ZA. Prenatal stress produces deficits in socio-sexual behavior of cycling, but not hormone-primed, Long-Evans rats. *Pharmacol Biochem Behav* 73: 53–60, 2002.

165. Fulford AJ, Marsden CA. Effect of isolation-rearing on noradrenaline release in rat hypothalamus and hippocampus in vitro. *Brain Res* 748: 93–99, 1997.

166. Garcia-Mesa Y, Gimenez-Llort L, Lopez LC, Venegas C, Cristofol R, Escames G, Acuna-Castroviejo D, Sanfeliu C. Melatonin plus physical exercise are highly neuroprotective in the 3xTg-AD mouse. *Neurobiol Aging* 33: 1124 e1113–1129, 2012.

167. Garibotto V, Borroni B, Kalbe E, Herholz K, Salmon E, Holtoff V, Sorbi S, Cappa SF, Padovani A, Fazio F, Perani D. Education and occupation as proxies for reserve in aMCI converters and AD: FDG-PET evidence. *Neurology* 71: 1342–1349, 2008.

168. Garrett KD, Browndyke JN, Whelihan W, Paul RH, DiCarlo M, Moser DJ, Cohen RA, Ott BR. The neuropsychological profile of vascular cognitive impairment–no dementia: comparisons to patients at risk for cerebrovascular disease and vascular dementia. *Arch Clin Neuropsychol* 19: 745–757, 2004.

169. Garrett KD, Paul RH, Libon DJ, Cohen RA. Defining the diagnosis of vascular dementia. *Appl Neuropsychol* 11: 204–209, 2004.

170. Gasparini L, Xu H. Potential roles of insulin and IGF-1 in Alzheimer's disease. *Trends Neurosci* 26: 404–406, 2003.

171. Gazzaley AH, Thakker MM, Hof PR, Morrison JH. Preserved number of entorhinal cortex layer II neurons in aged macaque monkeys. *Neurobiol Aging* 18: 549–553, 1997.

172. Gianfranceschi L, Siciliano R, Walls J, Morales B, Kirkwood A, Huang ZJ, Tonegawa S, Maffei L. Visual cortex is rescued from the effects of dark rearing by overexpression of BDNF. *Proc Natl Acad Sci USA* 100: 12486–12491, 2003.

173. Globus A, Rosenzweig MR, Bennett EL, Diamond MC. Effects of differential experience on dendritic spine counts in rat cerebral cortex. *J Comp Physiol Psychol* 82: 175–181, 1973.

174. Glover V. Annual Research Review: prenatal stress and the origins of psychopathology: an evolutionary perspective. *J Child Psychol Psychiatry* 52: 356–367, 2011.

175. Goard M, Dan Y. Basal forebrain activation enhances cortical coding of natural scienes. *Nat Neurosci* 12: 1444–1449, 2009.

176. Gogolla N, Caroni P, Luthi A, Herry C. Perineuronal nets protect fear memories from erasure. *Science* 325: 1258–1261, 2009.

177. Gould E, Reeves AJ, Fallah M, Tanapat P, Gross CG, Fuchs E. Hippocampal neurogenesis in adult Old World primates. *Proc Natl Acad Sci USA* 96: 5263–5267, 1999.

178. Graff J, Kim D, Dobbin MM, Tsai LH. Epigenetic regulation of gene expression in physiological and pathological brain processes. *Physiol Rev* 91: 603–649, 2011.

179. Graff J, Rei D, Guan JS, Wang WY, Seo J, Hennig KM, Nieland TJ, Fass DM, Kao PF, Kahn M, Su SC, Samiei A, Joseph N, Haggarty SJ, Delalle I, Tsai LH. An epigenetic blockade of cognitive functions in the neurodegenerating brain. *Nature* 483: 222–226, 2012.

180. Gramsbergen A, Mulder EJ. The influence of betamethasone and dexamethasone on motor development in young rats. *Pediatr Res* 44: 105–110, 1998.

181. Graupner M, Brunel N. Calcium-based plasticity model explains sensitivity of synaptic changes to spike pattern, rate, and dendritic location. *Proc Natl Acad Sci USA* 109: 3991–3996, 2012.

182. Green CS, Bavelier D. Learning, attentional control, and action video games. *Curr Biol* 22: R197–206, 2012.

183. Green EJ, Greenough WT. Altered synaptic transmission in dentate gyrus of rats reared in complex environments: evidence from hippocampal slices maintained in vitro. *J Neurophysiol* 55: 739–750, 1986.

184. Greenough WT, Volkmar FR. Pattern of dendritic branching in occipital cortex of rats reared in complex environments. *Exp Neurol* 40: 491–504, 1973.

185. Greenough WT, Volkmar FR, Juraska JM. Effects of rearing complexity on dendritic branching in frontolateral and temporal cortex of the rat. *Exp Neurol* 41: 371–378, 1973.

186. Gu Q. Neuromodulatory transmitter systems in the cortex and their role in cortical plasticity. *Neuroscience* 111: 815–835, 2002.

187. Gueneau G, Privat A, Drouet J, Court L. Subgranular zone of the dentate gyrus of young rabbits as a secondary matrix. A high-resolution autoradiographic study. *Dev Neurosci* 5: 345–358, 1982.

188. Guzzetta A, Baldini S, Bancale A, Baroncelli L, Ciucci F, Ghirri P, Putignano E, Sale A, Viegi A, Berardi N, Boldrini A, Cioni G, Maffei L. Massage accelerates brain development and the maturation of visual function. *J Neurosci* 29: 6042–6051, 2009.

189. Guzzetta A, D'Acunto MG, Carotenuto M, Berardi N, Bancale A, Biagioni E, Boldrini A, Ghirri P, Maffei L, Cioni G. The effects of preterm infant massage on brain electrical activity. *Dev Med Child Neurol* 53 Suppl 4: 46–51, 2011.

190. Haakstad LA, Bo K. Exercise in pregnant women and birth weight: a randomized controlled trial. *BMC Pregnancy Childbirth* 11: 66, 2011.

191. Hagberg B, Aicardi J, Dias K, Ramos O. A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of 35 cases. *Ann Neurol* 14: 471–479, 1983.

192. Harauzov A, Spolidoro M, DiCristo G, De Pasquale R, Cancedda L, Pizzorusso T, Viegi A, Berardi N, Maffei L. Reducing intracortical inhibition in the adult visual cortex promotes ocular dominance plasticity. *J Neurosci* 30: 361–371, 2010.

193. Harlow HF, Dodsworth RO, Harlow MK. Total social isolation in monkeys. *Proc Natl Acad Sci USA* 54: 90–97, 1965.

194. Hartley CA, Phelps EA. Changing fear: the neurocircuitry of emotion regulation. *Neuropsychopharmacology* 35: 136–146, 2010.

195. He HY, Ray B, Dennis K, Quinlan EM. Experience-dependent recovery of vision following chronic deprivation amblyopia. *Nat Neurosci* 10: 1134–1136, 2007.

196. He S, Ma J, Liu N, Yu X. Early enriched environment promotes neonatal GABAergic neurotransmission and accelerates synapse maturation. *J Neurosci* 30: 7910–7916, 2010.

197. Hensch TK. Critical period plasticity in local cortical circuits. *Nature Rev* 6: 877–888, 2005.

198. Hensch TK. Critical period regulation. *Annu Rev Neurosci* 27: 549–579, 2004.

199. Herring A, Ambree O, Tomm M, Habermann H, Sachser N, Paulus W, Keyvani K. Environmental enrichment enhances cellular plasticity in transgenic mice with Alzheimer-like pathology. *Exp Neurol* 216: 184–192, 2009.

200. Herring A, Donath A, Yarmolenko M, Uslar E, Conzen C, Kanakis D, Bosma C, Worm K, Paulus W, Keyvani K. Exercise during pregnancy mitigates Alzheimer-like pathology in mouse offspring. *FASEB J* 26: 117–128, 2012.

201. Heuninckx S, Wenderoth N, Swinnen SP. Systems neuroplasticity in the aging brain: recruiting additional neural resources for successful motor performance in elderly persons. *J Neurosci* 28: 91–99, 2008.

202. Heynen AJ, Yoon BJ, Liu CH, Chung HJ, Huganir RL, Bear MF. Molecular mechanism for loss of visual cortical responsiveness following brief monocular deprivation. *Nat Neurosci* 6: 854–862, 2003.

203. Hobson JA, McCarley RW, Wyzinski PW. Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. *Science* 189: 55–58, 1975.

204. Hofer MA. Hidden regulators in attachment, separation, and loss. *Monogr Soc Res Child Dev* 59: 192–207, 1994.

205. Hofer MA. On the nature and consequences of early loss. *Psychosom Med* 58: 570–581, 1996.

206. Hofer MA. Relationships as regulators: a psychobiologic perspective on bereavement. *Psychosom Med* 46: 183–197, 1984.

207. Hofer SB, Mrsic-Flogel TD, Bonhoeffer T, Hubener M. Experience leaves a lasting structural trace in cortical circuits. *Nature* 457: 313–317, 2009.

208. Hofer SB, Mrsic-Flogel TD, Bonhoeffer T, Hubener M. Lifelong learning: ocular dominance plasticity in mouse visual cortex. *Curr Opin Neurobiol* 16: 451–459, 2006.

209. Holden HM, Gilbert PE. Less efficient pattern separation may contribute to age-related spatial memory deficits. *Front Aging Neurosci* 4: 9, 2012.

210. Holloway RL Jr. Dendritic branching: some preliminary results of training and complexity in rat visual cortex. *Brain Res* 2: 393–396, 1966.

211. Holmes JM, Clarke MP. Amblyopia. *Lancet* 367: 1343–1351, 2006.

212. Hopkins SA, Baldi JC, Cutfield WS, McCowan L, Hofman PL. Effects of exercise training on maternal hormonal changes in pregnancy. *Clin Endocrinol* 74: 495–500, 2011.

213. Hu YS, Xu P, Pigino G, Brady ST, Larson J, Lazarov O. Complex environment experience rescues impaired neurogenesis, enhances synaptic plasticity, and attenuates neuropathology in familial Alzheimer's disease-linked APPswe/PS1DeltaE9 mice. *FASEB J* 24: 1667–1681, 2010.

214. Huang ZJ, Kirkwood A, Pizzorusso T, Porciatti V, Morales B, Bear MF, Maffei L, Tonegawa S. BDNF regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex. *Cell* 98: 739–755, 1999.

215. Hunt DL, Castillo PE. Synaptic plasticity of NMDA receptors: mechanisms and functional implications. *Curr Opin Neurobiol* 22: 496–508, 2012.

216. Ibi D, Takuma K, Koike H, Mizoguchi H, Tsuritani K, Kuwahara Y, Kamei H, Nagai T, Yoneda Y, Nabeshima T, Yamada K. Social isolation rearing-induced impairment of the hippocampal neurogenesis is associated with deficits in spatial memory and emotion-related behaviors in juvenile mice. *J Neurochem* 105: 921–932, 2008.

217. Ickes BR, Pham TM, Sanders LA, Albeck DS, Mohammed AH, Granholm AC. Long-term environmental enrichment leads to regional increases in neurotrophin levels in rat brain. *Exp Neurol* 164: 45–52, 2000.

218. Isaacs KR, Anderson BJ, Alcantara AA, Black JE, Greenough WT. Exercise and the brain: angiogenesis in the adult rat cerebellum after vigorous physical activity and motor skill learning. *J Cereb Blood Flow Metab* 12: 110–119, 1992.

219. Isgor C, Kabbaj M, Akil H, Watson SJ. Delayed effects of chronic variable stress during peripubertal-juvenile period on hippocampal morphology and on cognitive and stress axis functions in rats. *Hippocampus* 14: 636–648, 2004.

220. Jack CR Jr, Shiung MM, Weigand SD, O'Brien PC, Gunter JL, Boeve BF, Knopman DS, Smith GE, Ivnik RJ, Tangalos EG, Petersen RC. Brain atrophy rates predict subsequent clinical conversion in normal elderly and amnestic MCI. *Neurology* 65: 1227–1231, 2005.

221. Jacobsen JS, Wu CC, Redwine JM, Comery TA, Arias R, Bowlby M, Martone R, Morrison JH, Pangalos MN, Reinhart PH, Bloom FE. Early-onset behavioral and synaptic deficits in a mouse model of Alzheimer's disease. *Proc Natl Acad Sci USA* 103: 5161–5166, 2006.

222. Jakkamsetti V, Chang KQ, Kilgard MP. Reorganization in processing of spectral and temporal input in the rat posterior auditory field induced by environmental enrichment. *J Neurophysiol* 107: 1457–1475, 2012.

223. Jankowsky JL, Melnikova T, Fadale DJ, Xu GM, Slunt HH, Gonzales V, Younkin LH, Younkin SG, Borchelt DR, Savonenko AV. Environmental enrichment mitigates cognitive deficits in a mouse model of Alzheimer's disease. *J Neurosci* 25: 5217–5224, 2005.

224. Johansen JP, Cain CK, Ostroff LE, LeDoux JE. Molecular mechanisms of fear learning and memory. *Cell* 147: 509–524, 2011.

225. Johnson RA, Mitchell GS. Exercise-induced changes in hippocampal brain-derived neurotrophic factor and neurotrophin-3: effects of rat strain. *Brain Res* 983: 108–114, 2003.

226. Jones S, Laukka EJ, Small BJ, Fratiglioni L, Backman L. A preclinical phase in vascular dementia: cognitive impairment three years before diagnosis. *Dement Geriatr Cogn Disord* 18: 233–239, 2004.

227. Katzman R. Education and the prevalence of dementia and Alzheimer's disease. *Neurology* 43: 13–20, 1993.

228. Kaufman J, Charney D. Effects of early stress on brain structure and function: implications for understanding the relationship between child maltreatment and depression. *Dev Psychopathol* 13: 451–471, 2001.

229. Kempermann G, Fabel K, Ehninger D, Babu H, Leal-Galicia P, Garthe A, Wolf SA. Why and how physical activity promotes experience-induced brain plasticity. *Front Neurosci* 4: 189, 2010.

230. Kempermann G, Gast D, Gage FH. Neuroplasticity in old age: sustained fivefold induction of hippocampal neurogenesis by long-term environmental enrichment. *Ann Neurol* 52: 135–143, 2002.

231. Kempermann G, Kuhn HG, Gage FH. Experience-induced neurogenesis in the senescent dentate gyrus. *J Neurosci* 18: 3206–3212, 1998.

232. Kempermann G, Kuhn HG, Gage FH. More hippocampal neurons in adult mice living in an enriched environment. *Nature* 386: 493–495, 1997.

233. Kempermann G, Wiskott L, Gage FH. Functional significance of adult neurogenesis. *Curr Opin Neurobiol* 14: 186–191, 2004.

234. Kerr AL, Steuer EL, Pochtarev V, Swain RA. Angiogenesis but not neurogenesis is critical for normal learning and memory acquisition. *Neuroscience* 171: 214–226, 2010.

235. Keshet I, Yisraeli J, Cedar H. Effect of regional DNA methylation on gene expression. *Proc Natl Acad Sci USA* 82: 2560–2564, 1985.

236. Keyvani K, Sachser N, Witte OW, Paulus W. Gene expression profiling in the intact and injured brain following environmental enrichment. *J Neuropathol Exp Neurol* 63: 598–609, 2004.

237. Kilgard MP, Merzenich MM. Cortical map reorganization enabled by nucleus basalis activity. *Science* 279: 1714–1718, 1998.

238. Kim JH, Richardson R. New findings on extinction of conditioned fear early in development: theoretical and clinical implications. *Biol Psychiatry* 67: 297–303, 2010.

239. Kiorpes L. Visual processing in amblyopia: animal studies. *Strabismus* 14: 3–10, 2006.

240. Kirkwood A, Bear MF. Hebbian synapses in visual cortex. *J Neurosci* 14: 1634–1645, 1994.

241. Kleschevnikov AM, Belichenko PV, Faizi M, Jacobs LF, Htun K, Shamloo M, Mobley WC. Deficits in cognition and synaptic plasticity in a mouse model of Down syndrome ameliorated by $GABA_B$ receptor antagonists. *J Neurosci* 32: 9217–9227, 2012.

242. Kleschevnikov AM, Belichenko PV, Villar AJ, Epstein CJ, Malenka RC, Mobley WC. Hippocampal long-term potentiation suppressed by increased inhibition in the Ts65Dn mouse, a genetic model of Down syndrome. *J Neurosci* 24: 8153–8160, 2004.

243. Klintsova AY, Cowell RM, Swain RA, Napper RM, Goodlett CR, Greenough WT. Therapeutic effects of complex motor training on motor performance deficits induced by neonatal binge-like alcohol exposure in rats. I. Behavioral results. *Brain Res* 800: 48–61, 1998.

244. Klintsova AY, Dickson E, Yoshida R, Greenough WT. Altered expression of BDNF and its high-affinity receptor TrkB in response to complex motor learning and moderate exercise. *Brain Res* 1028: 92–104, 2004.

245. Knoth R, Singec I, Ditter M, Pantazis G, Capetian P, Meyer RP, Horvat V, Volk B, Kempermann G. Murine features of neurogenesis in the human hippocampus across the lifespan from 0 to 100 years. *PLoS One* 5: e8809, 2010.

246. Knudsen EI. Sensitive periods in the development of the brain and behavior. *J Cogn Neurosci* 16: 1412–1425, 2004.

247. Kobayashi S, Ohashi Y, Ando S. Effects of enriched environments with different durations and starting times on learning capacity during aging in rats assessed by a refined procedure of the Hebb-Williams maze task. *J Neurosci Res* 70: 340–346, 2002.

248. Kofman O. The role of prenatal stress in the etiology of developmental behavioural disorders. *Neurosci Biobehav Rev* 26: 457–470, 2002.

249. Kohl Z, Kuhn HG, Cooper-Kuhn CM, Winkler J, Aigner L, Kempermann G. Preweaning enrichment has no lasting effects on adult hippocampal neurogenesis in four-month-old mice. *Genes Brain Behav* 1: 46–54, 2002.

250. Koo JW, Park CH, Choi SH, Kim NJ, Kim HS, Choe JC, Suh YH. The postnatal environment can counteract prenatal effects on cognitive ability, cell proliferation, and synaptic protein expression. *FASEB J* 17: 1556–1558, 2003.

251. Koopmans GC, Brans M, Gomez-Pinilla F, Duis S, Gispen WH, Torres-Aleman I, Joosten EA, Hamers FP. Circulating insulin-like growth factor I and functional recovery from spinal cord injury under enriched housing conditions. *Eur J Neurosci* 23: 1035–1046, 2006.

252. Korb E, Finkbeiner S. Arc in synaptic plasticity: from gene to behavior. *Trends Neurosci* 34: 591–598, 2011.

253. Kozorovitskiy Y, Gross CG, Kopil C, Battaglia L, McBreen M, Stranahan AM, Gould E. Experience induces structural and biochemical changes in the adult primate brain. *Proc Natl Acad Sci USA* 102: 17478–17482, 2005.

254. Kramer AF, Erickson KI. Capitalizing on cortical plasticity: influence of physical activity on cognition and brain function. *Trends Cogn Sci* 11: 342–348, 2007.

255. Kramer AF, Erickson KI, Colcombe SJ. Exercise, cognition, and the aging brain. *J Appl Physiol* 101: 1237–1242, 2006.

256. Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, Chason J, Vakil E, Bardell L, Boileau RA, Colcombe A. Ageing, fitness and neurocognitive function. *Nature* 400: 418–419, 1999.

257. Kuhn CM, Schanberg SM. Responses to maternal separation: mechanisms and mediators. *Int J Dev Neurosci* 16: 261–270, 1998.

258. Kuhn HG, Dickinson-Anson H, Gage FH. Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. *J Neurosci* 16: 2027–2033, 1996.

259. Kulesskaya N, Rauvala H, Voikar V. Evaluation of social and physical enrichment in modulation of behavioural phenotype in C57BL/6J female mice. *PLoS One* 6: e24755, 2011.

260. Kumar A, Foster T. Environmental enrichment decreases the afterhyperpolarization in senescent rats. *Brain Res* 1130: 103–107, 2007.

261. Kumar A, Rani A, Tchigranova O, Lee WH, Foster TC. Influence of late-life exposure to environmental enrichment or exercise on hippocampal function and CA1 senescent physiology. *Neurobiol Aging* 33: 828 e821–817, 2012.

262. Ladd CO, Huot RL, Thrivikraman KV, Nemeroff CB, Meaney MJ, Plotsky PM. Long-term behavioral and neuroendocrine adaptations to adverse early experience. *Prog Brain Res* 122: 81–103, 2000.

263. Landau SM, Marks SM, Mormino EC, Rabinovici GD, Oh H, O'Neil JP, Wilson RS, Jagust WJ. Association of lifetime cognitive engagement and low beta-amyloid deposition. *Arch Neurol* 69: 623–629, 2012.

264. Landers MS, Knott GW, Lipp HP, Poletaeva I, Welker E. Synapse formation in adult barrel cortex following naturalistic environmental enrichment. *Neuroscience* 199: 143–152, 2011.

265. Landfield PW, Pitler TA. Prolonged Ca^{2+}-dependent afterhyperpolarizations in hippocampal neurons of aged rats. *Science* 226: 1089–1092, 1984.

266. Landi S, Cenni MC, Maffei L, Berardi N. Environmental enrichment effects on development of retinal ganglion cell dendritic stratification require retinal BDNF. *PLoS One* 2: e346, 2007.

267. Landi S, Ciucci F, Maffei L, Berardi N, Cenni MC. Setting the pace for retinal development: environmental enrichment acts through insulin-like growth factor 1 and brain-derived neurotrophic factor. *J Neurosci* 29: 10809–10819, 2009.

268. Landi S, Sale A, Berardi N, Viegi A, Maffei L, Cenni MC. Retinal functional development is sensitive to environmental enrichment: a role for BDNF. *FASEB J* 21: 130–139, 2007.

269. Larsson F, Winblad B, Mohammed AH. Psychological stress and environmental adaptation in enriched vs. impoverished housed rats. *Pharmacol Biochem Behav* 73: 193–207, 2002.

270. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch neurol* 58: 498–504, 2001.

271. Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, Greenop KR, Almeida OP. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA* 300: 1027–1037, 2008.

272. Laviola G, Rea M, Morley-Fletcher S, Di Carlo S, Bacosi A, De Simone R, Bertini M, Pacifici R. Beneficial effects of enriched environment on adolescent rats from stressed pregnancies. *Eur J Neurosci* 20: 1655–1664, 2004.

273. Lazarov O, Robinson J, Tang YP, Hairston IS, Korade-Mirnics Z, Lee VM, Hersh LB, Sapolsky RM, Mirnics K, Sisodia SS. Environmental enrichment reduces Abeta levels and amyloid deposition in transgenic mice. *Cell* 120: 701–713, 2005.

274. Lee HH, Kim H, Lee JW, Kim YS, Yang HY, Chang HK, Lee TH, Shin MC, Lee MH, Shin MS, Park S, Baek S, Kim CJ. Maternal swimming during pregnancy enhances short-term memory and neurogenesis in the hippocampus of rat pups. *Brain Dev* 28: 147–154, 2006.

275. Lejeune J. The 21 trisomy–current stage of chromosomal research. *Prog Med Genet* 23: 144–177, 1964.

276. Leslie JH, Nedivi E. Activity-regulated genes as mediators of neural circuit plasticity. *Prog Neurobiol* 94: 223–237, 2011.

277. Lesne S, Koh MT, Kotilinek L, Kayed R, Glabe CG, Yang A, Gallagher M, Ashe KH. A specific amyloid-beta protein assembly in the brain impairs memory. *Nature* 440: 352–357, 2006.

278. Lester BM, Tronick E, Nestler E, Abel T, Kosofsky B, Kuzawa CW, Marsit CJ, Maze I, Meaney MJ, Monteggia LM, Reul JM, Skuse DH, Sweatt JD, Wood MA. Behavioral epigenetics. *Ann NY Acad Sci* 1226: 14–33, 2011.

279. Levelt CN, Hubener M. Critical-period plasticity in the visual cortex. *Annu Rev Neurosci* 35: 309–330, 2012.

280. Levi DM, Hariharan S, Klein SA. Suppressive and facilitatory spatial interactions in amblyopic vision. *Vision Res* 42: 1379–1394, 2002.

281. Levi DM, Li RW. Improving the performance of the amblyopic visual system. *Philos Trans R Soc Lond B Biol Sci* 364: 399–407, 2009.

282. Li RW, Ngo C, Nguyen J, Levi DM. Video-game play induces plasticity in the visual system of adults with amblyopia. *PLoS Biol* 9: e1001135, 2011.

283. Li S, Jin M, Zhang D, Yang T, Koeglsperger T, Fu H, Selkoe DJ. Environmental novelty activates beta2-adrenergic signaling to prevent the impairment of hippocampal LTP by Abeta oligomers. *Neuron* 77: 929–941, 2013.

284. Li S, Shankar GM, Selkoe DJ. How do soluble oligomers of amyloid beta-protein impair hippocampal synaptic plasticity? *Front Cell Neurosci* 4: 5, 2010.

285. Lieberwirth C, Liu Y, Jia X, Wang Z. Social isolation impairs adult neurogenesis in the limbic system and alters behaviors in female prairie voles. *Horm Behav* 62: 357–366, 2012.

286. Lisman J, Yasuda R, Raghavachari S. Mechanisms of CaMKII action in long-term potentiation. *Nat Rev Neurosci* 13: 169–182, 2012.

287. Lista I, Sorrentino G. Biological mechanisms of physical activity in preventing cognitive decline. *Cell Mol Neurobiol* 30: 493–503, 2010.

288. Liu-Yesucevitz L, Bassell GJ, Gitler AD, Hart AC, Klann E, Richter JD, Warren ST, Wolozin B. Local RNA translation at the synapse and in disease. *J Neurosci* 31: 16086–16093, 2011.

289. Liu D, Diorio J, Day JC, Francis DD, Meaney MJ. Maternal care, hippocampal synaptogenesis and cognitive development in rats. *Nat Neurosci* 3: 799–806, 2000.

290. Liu D, Diorio J, Tannenbaum B, Caldji C, Francis D, Freedman A, Sharma S, Pearson D, Plotsky PM, Meaney MJ. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. *Science* 277: 1659–1662, 1997.

291. Liu N, He S, Yu X. Early natural stimulation through environmental enrichment accelerates neuronal development in the mouse dentate gyrus. *PLoS One* 7: e30803, 2012.

292. Llorens-Martin MV, Rueda N, Tejeda GS, Florez J, Trejo JL, Martinez-Cue C. Effects of voluntary physical exercise on adult hippocampal neurogenesis and behavior of Ts65Dn mice, a model of Down syndrome. *Neuroscience* 171: 1228–1240, 2010.

293. Lonetti G, Angelucci A, Morando L, Boggio EM, Giustetto M, Pizzorusso T. Early environmental enrichment moderates the behavioral and synaptic phenotype of MeCP2 null mice. *Biol Psychiatry* 67: 657–665, 2010.

294. Lordi B, Protais P, Mellier D, Caston J. Acute stress in pregnant rats: effects on growth rate, learning, and memory capabilities of the offspring. *Physiol Behav* 62: 1087–1092, 1997.

295. Lu L, Bao G, Chen H, Xia P, Fan X, Zhang J, Pei G, Ma L. Modification of hippocampal neurogenesis and neuroplasticity by social environments. *Exp Neurol* 183: 600–609, 2003.

296. Luby JL, Barch DM, Belden A, Gaffrey MS, Tillman R, Babb C, Nishino T, Suzuki H, Botteron KN. Maternal support in early childhood predicts larger hippocampal volumes at school age. *Proc Natl Acad Sci USA* 109: 2854–2859, 2012.

297. Lupien SJ, Fiocco A, Wan N, Maheu F, Lord C, Schramek T, Tu MT. Stress hormones and human memory function across the lifespan. *Psychoneuroendocrinology* 30: 225–242, 2005.

298. Lynch MA. Long-term potentiation and memory. *Physiol Rev* 84: 87–136, 2004.

299. Lyons MR, West AE. Mechanisms of specificity in neuronal activity-regulated gene transcription. *Prog Neurobiol* 94: 259–295, 2011.

300. Maestripieri D, Lindell SG, Higley JD. Intergenerational transmission of maternal behavior in rhesus macaques and its underlying mechanisms. *Dev Psychobiol* 49: 165–171, 2007.

301. Magee JC, Johnston D. A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. *Science* 275: 209–213, 1997.

302. Mainardi M, Landi S, Gianfranceschi L, Baldini S, De Pasquale R, Berardi N, Maffei L, Caleo M. Environmental enrichment potentiates thalamocortical transmission and plasticity in the adult rat visual cortex. *J Neurosci Res* 88: 3048–3059, 2010.

303. Mainardi M, Scabia G, Vottari T, Santini F, Pinchera A, Maffei L, Pizzorusso T, Maffei M. A sensitive period for environmental regulation of eating behavior and leptin sensitivity. *Proc Natl Acad Sci USA* 107: 16673–16678, 2010.

304. Majdan M, Shatz CJ. Effects of visual experience on activity-dependent gene regulation in cortex. *Nat Neurosci* 9: 650–659, 2006.

305. Makara JK, Losonczy A, Wen Q, Magee JC. Experience-dependent compartmentalized dendritic plasticity in rat hippocampal CA1 pyramidal neurons. *Nat Neurosci* 12: 1485–1487, 2009.

306. Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. *Neuron* 44: 5–21, 2004.

307. Malenka RC, Nicoll RA. Learning and memory. Never fear, LTP is hear. *Nature* 390: 552–553, 1997.

308. Malik R, Chattarji S. Enhanced intrinsic excitability and EPSP-spike coupling accompany enriched environment-induced facilitation of LTP in hippocampal CA1 pyramidal neurons. *J Neurophysiol* 107: 1366–1378.

309. Malik R, Chattarji S. Enhanced intrinsic excitability and EPSP-spike coupling accompany enriched environment-induced facilitation of LTP in hippocampal CA1 pyramidal neurons. *J Neurophysiol* 107: 1366–1378, 2012.

310. Markram H, Lubke J, Frotscher M, Sakmann B. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* 275: 213–215, 1997.

311. Marlatt MW, Potter MC, Lucassen PJ, van Praag H. Running throughout middle-age improves memory function, hippocampal neurogenesis, and BDNF levels in female C57BL/6J mice. *Dev Neurobiol* 72: 943–952, 2012.

312. Marlatt MW, Potter MC, Lucassen PJ, van Praag H. Running throughout middle-age improves memory function, hippocampal neurogenesis, and BDNF levels in female C57BL/6J mice. *Dev Neurobiol* 72: 943–952.

313. Marsden CA, King MV, Fone KC. Influence of social isolation in the rat on serotonergic function and memory–relevance to models of schizophrenia and the role of 5-HT(6) receptors. *Neuropharmacology* 61: 400–407, 2011.

314. Martinez-Cue C, Baamonde C, Lumbreras M, Paz J, Davisson MT, Schmidt C, Dierssen M, Florez J. Differential effects of environmental enrichment on behavior and learning of male and female Ts65Dn mice, a model for Down syndrome. *Behav Brain Res* 134: 185–200, 2002.

315. Martinez-Cue C, Rueda N, Garcia E, Davisson MT, Schmidt C, Florez J. Behavioral, cognitive and biochemical responses to different environmental conditions in male Ts65Dn mice, a model of Down syndrome. *Behav Brain Res* 163: 174–185, 2005.

316. Marx J. Alzheimer's disease. Play and exercise protect mouse brain from amyloid buildup. *Science* 307: 1547, 2005.

317. Maya-Vetencourt JF, Baroncelli L, Viegi A, Tiraboschi E, Castren E, Cattaneo A, Maffei L. IGF-1 restores visual cortex plasticity in adult life by reducing local GABA levels. *Neural Plast* 2012: 250421, 2012.

318. Maya Vetencourt JF, Sale A, Viegi A, Baroncelli L, De Pasquale R, O'Leary OF, Castren E, Maffei L. The antidepressant fluoxetine restores plasticity in the adult visual cortex. *Science* 320: 385–388, 2008.

319. Maya Vetencourt JF, Tiraboschi E, Spolidoro M, Castren E, Maffei L. Serotonin triggers a transient epigenetic mechanism that reinstates adult visual cortex plasticity in rats. *Eur J Neurosci* 33: 49–57, 2011.

320. Mayford M, Siegelbaum SA, Kandel ER. Synapses and memory storage. *Cold Spring Harb Perspect Biol* 4: 2012.

321. McGowan PO, Meaney MJ, Szyf M. Diet and the epigenetic (re)programming of phenotypic differences in behavior. *Brain Res* 1237: 12–24, 2008.

322. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonte B, Szyf M, Turecki G, Meaney MJ. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci* 12: 342–348, 2009.

323. McOmish CE, Hannan AJ. Enviromimetics: exploring gene environment interactions to identify therapeutic targets for brain disorders. *Expert Opin Therapeutic Targets* 11: 899–913, 2007.

324. McQuaid RJ, Audet MC, Anisman H. Environmental enrichment in male CD-1 mice promotes aggressive behaviors and elevated corticosterone and brain norepinephrine activity in response to a mild stressor. *Stress* 15: 354–360, 2012.

325. McQuaid RJ, Audet MC, Jacobson-Pick S, Anisman H. The differential impact of social defeat on mice living in isolation or groups in an enriched environment: plasma corticosterone and monoamine variations. *Int J Neuropsychopharmacol* 1–13, 2013.

327. Meaney MJ, Diorio J, Francis D, Widdowson J, LaPlante P, Caldji C, Sharma S, Seckl JR, Plotsky PM. Early environmental regulation of forebrain glucocorticoid receptor gene expression: implications for adrenocortical responses to stress. *Dev Neurosci* 18: 49–72, 1996.

328. Meaney MJ, Szyf M. Maternal care as a model for experience-dependent chromatin plasticity? *Trends Neurosci* 28: 456–463, 2005.

329. Merabet LB, Pascual-Leone A. Neural reorganization following sensory loss: the opportunity of change. *Nat Rev Neurosci* 11: 44–52, 2010.

330. Merrill DA, Chiba AA, Tuszynski MH. Conservation of neuronal number and size in the entorhinal cortex of behaviorally characterized aged rats. *J Comp Neurol* 438: 445–456, 2001.

331. Merrill DA, Roberts JA, Tuszynski MH. Conservation of neuron number and size in entorhinal cortex layers II, III, and V/VI of aged primates. *J Comp Neurol* 422: 396–401, 2000.

332. Milgram NW, Zicker SC, Head E, Muggenburg BA, Murphey H, Ikeda-Douglas CJ, Cotman CW. Dietary enrichment counteracts age-associated cognitive dysfunction in canines. *Neurobiol Aging* 23: 737–745, 2002.

333. Minoshima S. Imaging Alzheimer's disease: clinical applications. *Neuroimaging Clin N Am* 13: 769–780, 2003.

334. Mirmiran M, van den Dungen H, Uylings HB. Sleep patterns during rearing under different environmental conditions in juvenile rats. *Brain Res* 233: 287–298, 1982.

335. Mlynarik M, Johansson BB, Jezova D. Enriched environment influences adrenocortical response to immune challenge and glutamate receptor gene expression in rat hippocampus. *Ann NY Acad Sci* 1018: 273–280, 2004.

336. Mollgaard K, Diamond MC, Bennett EL, Rosenzweig MR, Lindner B. Quantitative synaptic changes with differential experience in rat brain. *Int J Neurosci* 2: 113–127, 1971.

337. Moretti P, Levenson JM, Battaglia F, Atkinson R, Teague R, Antalffy B, Armstrong D, Arancio O, Sweatt JD, Zoghbi HY. Learning and memory and synaptic plasticity are impaired in a mouse model of Rett syndrome. *J Neurosci* 26: 319–327, 2006.

338. Morishita H, Hensch TK. Critical period revisited: impact on vision. *Curr Opin Neurobiol* 18: 101–107, 2008.

339. Morishita H, Miwa JM, Heintz N, Hensch TK. Lynx1, a cholinergic brake, limits plasticity in adult visual cortex. *Science* 330: 1238–1240, 2010.

340. Morley-Fletcher S, Rea M, Maccari S, Laviola G. Environmental enrichment during adolescence reverses the effects of prenatal stress on play behaviour and HPA axis reactivity in rats. *Eur J Neurosci* 18: 3367–3374, 2003.

341. Morris RG, Moser EI, Riedel G, Martin SJ, Sandin J, Day M, O'Carroll C. Elements of a neurobiological theory of the hippocampus: the role of activity-dependent synaptic plasticity in memory. *Philos Trans R Soc Lond B Biol Sci* 358: 773–786, 2003.

342. Moser MB, Trommald M, Egeland T, Andersen P. Spatial training in a complex environment and isolation alter the spine distribution differently in rat CA1 pyramidal cells. *J Comp Neurol* 380: 373–381, 1997.

343. Mrsic-Flogel TD, Hofer SB, Ohki K, Reid RC, Bonhoeffer T, Hubener M. Homeostatic regulation of eye-specific responses in visual cortex during ocular dominance plasticity. *Neuron* 54: 961–972, 2007.

344. Muchimapura S, Fulford AJ, Mason R, Marsden CA. Isolation rearing in the rat disrupts the hippocampal response to stress. *Neuroscience* 112: 697–705, 2002.

345. Mulder EJ, Robles de Medina PG, Huizink AC, Van den Bergh BR, Buitelaar JK, Visser GH. Prenatal maternal stress: effects on pregnancy and the (unborn) child. *Early Hum Dev* 70: 3–14, 2002.

346. Nagahara AH, Merrill DA, Coppola G, Tsukada S, Schroeder BE, Shaked GM, Wang L, Blesch A, Kim A, Conner JM, Rockenstein E, Chao MV, Koo EH, Geschwind D, Masliah E, Chiba AA, Tuszynski MH. Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease. *Nat Med* 15: 331–337, 2009.

347. Naka F, Shiga T, Yaguchi M, Okado N. An enriched environment increases noradrenaline concentration in the mouse brain. *Brain Res* 924: 124–126, 2002.

348. Nakashiba T, Cushman JD, Pelkey KA, Renaudineau S, Buhl DL, McHugh TJ, Rodriguez Barrera V, Chittajallu R, Iwamoto KS, McBain CJ, Fanselow MS, Tonegawa S. Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. *Cell* 149: 188–201, 2012.

349. Naumova OY, Lee M, Koposov R, Szyf M, Dozier M, Grigorenko EL. Differential patterns of whole-genome DNA methylation in institutionalized children and children raised by their biological parents. *Dev Psychopathol* 24: 143–155, 2012.

350. Neeper SA, Gomez-Pinilla F, Choi J, Cotman CW. Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. *Brain Res* 726: 49–56, 1996.

351. Nelson CA 3rd, Zeanah CH, Fox NA, Marshall PJ, Smyke AT, Guthrie D. Cognitive recovery in socially deprived young children: the Bucharest Early Intervention Project. *Science* 318: 1937–1940, 2007.

352. Nelson SB, Sjostrom PJ, Turrigiano GG. Rate and timing in cortical synaptic plasticity. *Philos Trans R Soc Lond B Biol Sci* 357: 1851–1857, 2002.

353. Nichol K, Deeny SP, Seif J, Camaclang K, Cotman CW. Exercise improves cognition and hippocampal plasticity in APOE epsilon4 mice. *Alzheimers Dement* 5: 287–294, 2009.

354. Niell CM, Stryker MP. Modulation of visual responses by behavioral state in mouse visual cortex. *Neuron* 65: 472–479, 2010.

355. Nithianantharajah J, Hannan AJ. Enriched environments, experience-dependent plasticity and disorders of the nervous system. *Nat Rev Neurosci* 7: 697–709, 2006.

356. Nithianantharajah J, Hannan AJ. The neurobiology of brain and cognitive reserve: mental and physical activity as modulators of brain disorders. *Prog Neurobiol* 89: 369–382, 2009.

357. Numan M. Hypothalamic neural circuits regulating maternal responsiveness toward infants. *Behav Cogn Neurosci Rev* 5: 163–190, 2006.

358. Nyhuis TJ, Masini CV, Sasse SK, Day HE, Campeau S. Physical activity, but not environmental complexity, facilitates HPA axis response habituation to repeated audiogenic stress despite neurotrophin mRNA regulation in both conditions. *Brain Res* 1362: 68–77, 2010.

359. O'Callaghan RM, Griffin EW, Kelly AM. Long-term treadmill exposure protects against age-related neurodegenerative change in the rat hippocampus. *Hippocampus* 19: 1019–1029, 2009.

360. Obiang P, Maubert E, Bardou I, Nicole O, Launay S, Bezin L, Vivien D, Agin V. Enriched housing reverses age-associated impairment of cognitive functions and tPA-dependent maturation of BDNF. *Neurobiol Learn Mem* 96: 121–129, 2011.

361. Oitzl MS, Workel JO, Fluttert M, Frosch F, De Kloet ER. Maternal deprivation affects behaviour from youth to senescence: amplification of individual differences in spatial learning and memory in senescent Brown Norway rats. *Eur J Neurosci* 12: 3771–3780, 2000.

362. Oliff HS, Berchtold NC, Isackson P, Cotman CW. Exercise-induced regulation of brain-derived neurotrophic factor (BDNF) transcripts in the rat hippocampus. *Brain Res* 61: 147–153, 1998.

363. Owen AM, Hampshire A, Grahn JA, Stenton R, Dajani S, Burns AS, Howard RJ, Ballard CG. Putting brain training to the test. *Nature* 465: 775–778, 2010.

364. Pacteau C, Einon D, Sinden J. Early rearing environment and dorsal hippocampal ibotenic acid lesions: long-term influences on spatial learning and alternation in the rat. *Behav Brain Res* 34: 79–96, 1989.

365. Paillard-Borg S, Fratiglioni L, Xu W, Winblad B, Wang HX. An active lifestyle postpones dementia onset by more than one year in very old adults. *J Alzheimers Dis* 31: 835–842, 2012.

366. Pakkenberg B, Gundersen HJ. Neocortical neuron number in humans: effect of sex and age. *J Comp Neurol* 384: 312–320, 1997.

367. Pakkenberg B, Pelvig D, Marner L, Bundgaard MJ, Gundersen HJ, Nyengaard JR, Regeur L. Aging and the human neocortex. *Exp Gerontol* 38: 95–99, 2003.

368. Palmer K, Backman L, Winblad B, Fratiglioni L. Mild cognitive impairment in the general population: occurrence and progression to Alzheimer disease. *Am J Geriatr Psychiatry* 16: 603–611, 2008.

369. Parachikova A, Nichol KE, Cotman CW. Short-term exercise in aged Tg2576 mice alters neuroinflammation and improves cognition. *Neurobiol Dis* 30: 121–129, 2008.

370. Park DC, Gutchess AH. Aging, cognition, and culture: a neuroscientific perspective. *Neurosci Biobehav Rev* 26: 859–867, 2002.

371. Park DC, Reuter-Lorenz P. The adaptive brain: aging and neurocognitive scaffolding. *Annu Rev Psychol* 60: 173–196, 2009.

372. Parker KJ, Buckmaster CL, Sundlass K, Schatzberg AF, Lyons DM. Maternal mediation, stress inoculation, and the development of neuroendocrine stress resistance in primates. *Proc Natl Acad Sci USA* 103: 3000–3005, 2006.

373. Parker KJ, Maestripieri D. Identifying key features of early stressful experiences that produce stress vulnerability and resilience in primates. *Neurosci Biobehav Rev* 35: 1466–1483, 2011.

374. Parnpiansil P, Jutapakdeegul N, Chentanez T, Kotchabhakdi N. Exercise during pregnancy increases hippocampal brain-derived neurotrophic factor mRNA expression and spatial learning in neonatal rat pup. *Neurosci Lett* 352: 45–48, 2003.

375. Pascale R, Simile MM, Ruggiu ME, Seddaiu MA, Satta G, Sequenza MJ, Daino L, Vannini MG, Lai P, Feo F. Reversal by 5-azacytidine of the S-adenosyl-L-methionine-induced inhibition of the development of putative preneoplastic foci in rat liver carcinogenesis. *Cancer Lett* 56: 259–265, 1991.

376. Pascual R, Figueroa H. Effects of preweaning sensorimotor stimulation on behavioral and neuronal development in motor and visual cortex of the rat. *Biol Neonate* 69: 399–404, 1996.

377. Pauk J, Kuhn CM, Field TM, Schanberg SM. Positive effects of tactile versus kinesthetic or vestibular stimulation on neuroendocrine and ODC activity in maternally-deprived rat pups. *Life Sci* 39: 2081–2087, 1986.

378. Paylor R, Morrison SK, Rudy JW, Waltrip LT, Wehner JM. Brief exposure to an enriched environment improves performance on the Morris water task and increases

hippocampal cytosolic protein kinase C activity in young rats. *Behav Brain Res* 52: 49–59, 1992.

379. Peleg S, Sananbenesi F, Zovoilis A, Burkhardt S, Bahari-Javan S, Agis-Balboa RC, Cota P, Wittnam JL, Gogol-Doering A, Opitz L, Salinas-Riester G, Dettenhofer M, Kang H, Farinelli L, Chen W, Fischer A. Altered histone acetylation is associated with age-dependent memory impairment in mice. *Science* 328: 753–756, 2010.

380. Peng S, Garzon DJ, Marchese M, Klein W, Ginsberg SD, Francis BM, Mount HT, Mufson EJ, Salehi A, Fahnestock M. Decreased brain-derived neurotrophic factor depends on amyloid aggregation state in transgenic mouse models of Alzheimer's disease. *J Neurosci* 29: 9321–9329, 2009.

381. Peng S, Wuu J, Mufson EJ, Fahnestock M. Precursor form of brain-derived neurotrophic factor and mature brain-derived neurotrophic factor are decreased in the pre-clinical stages of Alzheimer's disease. *J Neurochem* 93: 1412–1421, 2005.

382. Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, Sloan R, Gage FH, Brown TR, Small SA. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc Natl Acad Sci USA* 104: 5638–5643, 2007.

383. Perez-Cremades D, Hernandez S, Blasco-Ibanez JM, Crespo C, Nacher J, Varea E. Alteration of inhibitory circuits in the somatosensory cortex of Ts65Dn mice, a model for Down's syndrome. *J Neural Transm* 117: 445–455, 2010.

384. Peters A, Leahu D, Moss MB, McNally KJ. The effects of aging on area 46 of the frontal cortex of the rhesus monkey. *Cereb Cortex* 4: 621–635, 1994.

385. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 256: 183–194, 2004.

386. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B. Current concepts in mild cognitive impairment. *Arch Neurol* 58: 1985–1992, 2001.

387. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 56: 303–308, 1999.

388. Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 56: 1133–1142, 2001.

389. Petrosini L, De Bartolo P, Foti F, Gelfo F, Cutuli D, Leggio MG, Mandolesi L. On whether the environmental enrichment may provide cognitive and brain reserves. *Brain Res Rev* 61: 221–239, 2009.

390. Pham TM, Winblad B, Granholm AC, Mohammed AH. Environmental influences on brain neurotrophins in rats. *Pharmacol Biochem Behav* 73: 167–175, 2002.

391. Phillips HS, Hains JM, Armanini M, Laramee GR, Johnson SA, Winslow JW. BDNF mRNA is decreased in the hippocampus of individuals with Alzheimer's disease. *Neuron* 7: 695–702, 1991.

392. Pike KE, Savage G, Villemagne VL, Ng S, Moss SA, Maruff P, Mathis CA, Klunk WE, Masters CL, Rowe CC. Beta-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease. *Brain* 130: 2837–2844, 2007.

393. Pizzorusso T, Medini P, Berardi N, Chierzi S, Fawcett JW, Maffei L. Reactivation of ocular dominance plasticity in the adult visual cortex. *Science* 298: 1248–1251, 2002.

394. Pizzorusso T, Medini P, Landi S, Baldini S, Berardi N, Maffei L. Structural and functional recovery from early monocular deprivation in adult rats. *Proc Natl Acad Sci USA* 103: 8517–8522, 2006.

395. Podewils LJ, Guallar E, Kuller LH, Fried LP, Lopez OL, Carlson M, Lyketsos CG. Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. *Am J Epidemiol* 161: 639–651, 2005.

396. Polat U, Bonneh Y, Ma-Naim T, Belkin M, Sagi D. Spatial interactions in amblyopia: effects of stimulus parameters and amblyopia type. *Vision Res* 45: 1471–1479, 2005.

397. Polley DB, Kvasnak E, Frostig RD. Naturalistic experience transforms sensory maps in the adult cortex of caged animals. *Nature* 429: 67–71, 2004.

398. Poltyrev T, Keshet GI, Kay G, Weinstock M. Role of experimental conditions in determining differences in exploratory behavior of prenatally stressed rats. *Dev Psychobiol* 29: 453–462, 1996.

399. Pop V, Head E, Hill MA, Gillen D, Berchtold NC, Muggenburg BA, Milgram NW, Murphy MP, Cotman CW. Synergistic effects of long-term antioxidant diet and behavioral enrichment on beta-amyloid load and non-amyloidogenic processing in aged canines. *J Neurosci* 30: 9831–9839, 2010.

400. Prather H, Spitznagle T, Hunt D. Benefits of exercise during pregnancy. *PMR* 4: 845–850, 2012.

401. Prusky GT, Reidel C, Douglas RM. Environmental enrichment from birth enhances visual acuity but not place learning in mice. *Behav Brain Res* 114: 11–15, 2000.

402. Pryce CR, Feldon J. Long-term neurobehavioural impact of the postnatal environment in rats: manipulations, effects and mediating mechanisms. *Neurosci Biobehav Rev* 27: 57–71, 2003.

403. Putignano E, Lonetti G, Cancedda L, Ratto G, Costa M, Maffei L, Pizzorusso T. Developmental downregulation of histone posttranslational modifications regulates visual cortical plasticity. *Neuron* 53: 747–759, 2007.

404. Qiu X, Huang CX, Lu W, Yang S, Li C, Shi XY, Chen L, Xiu Y, Yang JQ, Tang Y. Effects of a 4month enriched environment on the hippocampus and the myelinated fibers in the hippocampus of middle-aged rats. *Brain Res* 1465: 26–33, 2012.

405. Qiu X, Li C, Jiang R, Chen L, Huang C, Yang S, Lu W, Shi X, Zhao Y, Gao Y, Cheng G, Tang Y. The effects of short-term enriched environment on capillaries of the middle-aged rat cortex. *Neurosci Lett* 505: 186–190, 2011.

406. Raine A, Mellingen K, Liu J, Venables P, Mednick SA. Effects of environmental enrichment at ages 3–5 years on schizotypal personality and antisocial behavior at ages 17 and 23 years. *Am J Psychiatry* 160: 1627–1635, 2003.

407. Raine A, Venables PH, Dalais C, Mellingen K, Reynolds C, Mednick SA. Early educational and health enrichment at age 3–5 years is associated with increased autonomic and central nervous system arousal and orienting at age 11 years: evidence from the Mauritius Child Health Project. *Psychophysiology* 38: 254–266, 2001.

408. Rampon C, Jiang CH, Dong H, Tang YP, Lockhart DJ, Schultz PG, Tsien JZ, Hu Y. Effects of environmental enrichment on gene expression in the brain. *Proc Natl Acad Sci USA* 97: 12880–12884, 2000.

409. Rampon C, Tang YP, Goodhouse J, Shimizu E, Kyin M, Tsien JZ. Enrichment induces structural changes and recovery from nonspatial memory deficits in CA1 NMDAR1-knockout mice. *Nat Neurosci* 3: 238–244, 2000.

410. Rasch B, Born J. About sleep's role in memory. *Physiol Rev* 93: 681–766, 2013.

411. Rashad MA. Pharmacological enhancement of treatment for amblyopia. *Clin Ophthalmol* 6: 409–416, 2012.

412. Rasmuson S, Olsson T, Henriksson BG, Kelly PA, Holmes MC, Seckl JR, Mohammed AH. Environmental enrichment selectively increases 5-HT_{1A} receptor mRNA expression and binding in the rat hippocampus. *Brain Res* 53: 285–290, 1998.

413. Raz N, Rodrigue KM, Head D, Kennedy KM, Acker JD. Differential aging of the medial temporal lobe: a study of a five-year change. *Neurology* 62: 433–438, 2004.

414. Razin A. CpG methylation, chromatin structure and gene silencing-a three-way connection. *EMBO J* 17: 4905–4908, 1998.

415. Razin A, Szyf M. DNA methylation patterns. Formation and function. *Biochim Biophys Acta* 782: 331–342, 1984.

416. Redolat R, Mesa-Gresa P. Potential benefits and limitations of enriched environments and cognitive activity on age-related behavioural decline. *Curr Top Behav Neurosci* 10: 293–316, 2012.

417. Riley KP, Snowdon DA, Desrosiers MF, Markesbery WR. Early life linguistic ability, late life cognitive function, and neuropathology: findings from the Nun Study. *Neurobiol Aging* 26: 341–347, 2005.

418. Rioult-Pedotti MS, Friedman D, Donoghue JP. Learning-induced LTP in neocortex. *Science* 290: 533–536, 2000.

419. Rissman RA, Mobley WC. Implications for treatment: $GABA_A$ receptors in aging, Down syndrome and Alzheimer's disease. *J Neurochem* 117: 613–622, 2011.

420. Rogan MT, Staubli UV, LeDoux JE. Fear conditioning induces associative long-term potentiation in the amygdala. *Nature* 390: 604–607, 1997.

421. Ronca AE, Lamkin CA, Alberts JR. Maternal contributions to sensory experience in the fetal and newborn rat (*Rattus norvegicus*). *J Comp Psychol* 107: 61–74, 1993.

422. Rosa BV, Firth EC, Blair HT, Vickers MH, Morel PC. Voluntary exercise in pregnant rats positively influences fetal growth without initiating a maternal physiological stress response. *Am J Physiol Regul Integr Comp Physiol* 300: R1134–R1141, 2011.

423. Rosenzweig MR. Modification of brain circuits through experience. In: *Neural Plasticity and Memory: From Genes to Brain Imaging. Frontiers in Neuroscience*, edited by F. Bérmudez-Rattoni, Boca Raton, FL: CRC, 2007.

424. Rosenzweig MR, Bennett EL. Psychobiology of plasticity: effects of training and experience on brain and behavior. *Behav Brain Res* 78: 57–65, 1996.

425. Rosenzweig MR, Bennett EL, Diamond MC. Effects of differential environments on brain anatomy and brain chemistry. *Proc Annu Meet Am Psychopathol Assoc* 56: 45–56, 1967.

426. Rosenzweig MR, Bennett EL, Hebert M, Morimoto H. Social grouping cannot account for cerebral effects of enriched environments. *Brain Res* 153: 563–576, 1978.

427. Rosenzweig MR, Bennett EL, Krech D. Cerebral *Effects of Environmental Complexity and Training among Adult Rats*. *J Comp Physiol Psychol* 57: 438–439, 1964.

428. Rosenzweig MR, Krech D, Bennett EL, Diamond MC. Effects of environmental complexity and training on brain chemistry and anatomy: a replication and extension. *J Comp Physiol Psychol* 55: 429–437, 1962.

429. Rossi C, Angelucci A, Costantin L, Braschi C, Mazzantini M, Babbini F, Fabbri ME, Tessarollo L, Maffei L, Berardi N, Caleo M. Brain-derived neurotrophic factor (BDNF) is required for the enhancement of hippocampal neurogenesis following environmental enrichment. *Eur J Neurosci* 24: 1850–1856, 2006.

430. Rossi S, Rossini PM. TMS in cognitive plasticity and the potential for rehabilitation. *Trends Cogn Sci* 8: 273–279, 2004.

431. Roy V, Belzung C, Delarue C, Chapillon P. Environmental enrichment in BALB/c mice: effects in classical tests of anxiety and exposure to a predatory odor. *Physiol Behav* 74: 313–320, 2001.

432. Ruscheweyh R, Willemer C, Kruger K, Duning T, Warnecke T, Sommer J, Volker K, Ho HV, Mooren F, Knecht S, Floel A. Physical activity and memory functions: an interventional study. *Neurobiol Aging* 32: 1304–1319, 2011.

433. Russo SJ, Murrough JW, Han MH, Charney DS, Nestler EJ. Neurobiology of resilience. *Nat Neurosci* 15: 1475–1484, 2012.

434. Sahay A, Scobie KN, Hill AS, O'Carroll CM, Kheirbek MA, Burghardt NS, Fenton AA, Dranovsky A, Hen R. Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature* 472: 466–470.

435. Sahay A, Scobie KN, Hill AS, O'Carroll CM, Kheirbek MA, Burghardt NS, Fenton AA, Dranovsky A, Hen R. Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature* 472: 466–470, 2011.

436. Sahay A, Wilson DA, Hen R. Pattern separation: a common function for new neurons in hippocampus and olfactory bulb. *Neuron* 70: 582–588, 2011.

437. Sale A, Berardi N, Maffei L. Enrich the environment to empower the brain. *Trends Neurosci* 32: 233–239, 2009.

438. Sale A, Berardi N, Spolidoro M, Baroncelli L, Maffei L. GABAergic inhibition in visual cortical plasticity. *Front Cell Neurosci* 4: 10, 2010.

440. Sale A, Cenni MC, Ciucci F, Putignano E, Chierzi S, Maffei L. Maternal enrichment during pregnancy accelerates retinal development of the fetus. *PLoS One* 2: e1160, 2007.

441. Sale A, De Pasquale R, Bonaccorsi J, Pietra G, Olivieri D, Berardi N, Maffei L. Visual perceptual learning induces long-term potentiation in the visual cortex. *Neuroscience* 172: 219–225, 2011.

443. Sale A, Maya Vetencourt JF, Medini P, Cenni MC, Baroncelli L, De Pasquale R, Maffei L. Environmental enrichment in adulthood promotes amblyopia recovery through a reduction of intracortical inhibition. *Nat Neurosci* 10: 679–681, 2007.

444. Sale A, Putignano E, Cancedda L, Landi S, Cirulli F, Berardi N, Maffei L. Enriched environment and acceleration of visual system development. *Neuropharmacology* 47: 649–660, 2004.

445. Sandi C. Stress, cognitive impairment and cell adhesion molecules. *Nat Rev Neurosci* 5: 917–930, 2004.

446. Saxe MD, Battaglia F, Wang JW, Malleret G, David DJ, Monckton JE, Garcia AD, Sofroniew MV, Kandel ER, Santarelli L, Hen R, Drew MR. Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus. *Proc Natl Acad Sci USA* 103: 17501–17506, 2006.

447. Scali M, Baroncelli L, Cenni MC, Sale A, Maffei L. A rich environmental experience reactivates visual cortex plasticity in aged rats. *Exp Gerontol* 47: 337–341, 2012.

448. Schanberg SM, Field TM. Sensory deprivation stress and supplemental stimulation in the rat pup and preterm human neonate. *Child Dev* 58: 1431–1447, 1987.

449. Scheiman MM, Hertle RW, Beck RW, Edwards AR, Birch E, Cotter SA, Crouch ER Jr, Cruz OA, Davitt BV, Donahue S, Holmes JM, Lyon DW, Repka MX, Sala NA, Silbert DI, Suh DW, Tamkins SM. Randomized trial of treatment of amblyopia in children aged 7 to 17 years. *Arch Ophthalmol* 123: 437–447, 2005.

450. Scheltens P, Fox N, Barkhof F, De Carli C. Structural magnetic resonance imaging in the practical assessment of dementia: beyond exclusion. *Lancet Neurol* 1: 13–21, 2002.

451. Schiller D, Monfils MH, Raio CM, Johnson DC, Ledoux JE, Phelps EA. Preventing the return of fear in humans using reconsolidation update mechanisms. *Nature* 463: 49–53, 2010.

452. Schubert MI, Porkess MV, Dashdorj N, Fone KC, Auer DP. Effects of social isolation rearing on the limbic brain: a combined behavioral and magnetic resonance imaging volumetry study in rats. *Neuroscience* 159: 21–30, 2009.

453. Segovia G, Yague AG, Garcia-Verdugo JM, Mora F. Environmental enrichment promotes neurogenesis and changes the extracellular concentrations of glutamate and GABA in the hippocampus of aged rats. *Brain Res Bull* 70: 8–14, 2006.

454. Shang NX, Zou LP, Zhao JB, Zhang F, Li H. Association between prenatal stress and infantile spasms: a case-control study in China. *Pediatr Neurol* 42: 181–186, 2010.

455. Shankar GM, Li S, Mehta TH, Garcia-Munoz A, Shepardson NE, Smith I, Brett FM, Farrell MA, Rowan MJ, Lemere CA, Regan CM, Walsh DM, Sabatini BL, Selkoe DJ. Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nat Med* 14: 837–842, 2008.

456. Siarey RJ, Carlson EJ, Epstein CJ, Balbo A, Rapoport SI, Galdzicki Z. Increased synaptic depression in the Ts65Dn mouse, a model for mental retardation in Down syndrome. *Neuropharmacology* 38: 1917–1920, 1999.

457. Siette J, Westbrook RF, Cotman C, Sidhu K, Zhu W, Sachdev P, Valenzuela MJ. Age-specific effects of voluntary exercise on memory and the older brain. *Biol Psychiatry* 73: 435–442, 2013.

458. Silingardi D, Scali M, Belluomini G, Pizzorusso T. Epigenetic treatments of adult rats promote recovery from visual acuity deficits induced by long-term monocular deprivation. *Eur J Neurosci* 31: 2185–2192, 2010.

459. Simonetti T, Lee H, Bourke M, Leamey CA, Sawatari A. Enrichment from birth accelerates the functional and cellular development of a motor control area in the mouse. *PLoS One* 4: e6780, 2009.

460. Sirevaag AM, Greenough WT. Differential rearing effects on rat visual cortex synapses. II. Synaptic morphometry. *Brain Res* 351: 215–226, 1985.

461. Sjostrom PJ, Turrigiano GG, Nelson SB. Rate, timing, and cooperativity jointly determine cortical synaptic plasticity. *Neuron* 32: 1149–1164, 2001.

462. Small BJ, Gagnon E, Robinson B. Early identification of cognitive deficits: preclinical Alzheimer's disease and mild cognitive impairment. *Geriatrics* 62: 19–23, 2007.

463. Small SA, Schobel SA, Buxton RB, Witter MP, Barnes CA. A pathophysiological framework of hippocampal dysfunction in ageing and disease. *Nat Rev Neurosci* 12: 585–601, 2011.

464. Smit-Rigter LA, Champagne DL, van Hooft JA. Lifelong impact of variations in maternal care on dendritic structure and function of cortical layer 2/3 pyramidal neurons in rat offspring. *PLoS One* 4: e5167, 2009.

465. Smith DE, Rapp PR, McKay HM, Roberts JA, Tuszynski MH. Memory impairment in aged primates is associated with focal death of cortical neurons and atrophy of subcortical neurons. *J Neurosci* 24: 4373–4381, 2004.

466. Soffie M, Hahn K, Terao E, Eclancher F. Behavioural and glial changes in old rats following environmental enrichment. *Behav Brain Res* 101: 37–49, 1999.

467. Solomon GF, Levine S, Kraft JK. Early experience and immunity. *Nature* 220: 821–822, 1968.

468. Spalding KL, Bergmann O, Alkass K, Bernard S, Salehpour M, Huttner HB, Bostrom E, Westerlund I, Vial C, Buchholz BA, Possnert G, Mash DC, Druid H, Frisen J. Dynamics of hippocampal neurogenesis in adult humans. *Cell* 153: 1219–1227, 2013.

469. Spolidoro M, Baroncelli L, Putignano E, Maya-Vetencourt JF, Viegi A, Maffei L. Food restriction enhances visual cortex plasticity in adulthood. *Nat Commun* 2: 320, 2011.

470. Spolidoro M, Putignano E, Munafo C, Maffei L, Pizzorusso T. Inhibition of matrix metalloproteinases prevents the potentiation of nondeprived-eye responses after monocular deprivation in juvenile rats. *Cereb Cortex* 22: 725–734, 2012.

471. Squire LR, Wixted JT. The cognitive neuroscience of human memory since HM. *Annu Rev Neurosci* 34: 259–288, 2011.

472. Stent GS. A physiological mechanism for Hebb's postulate of learning. *Proc Natl Acad Sci USA* 70: 997–1001, 1973.

473. Stern Y. Cognitive reserve. *Neuropsychologia* 47: 2015–2028, 2009.

474. Sultan FA, Day JJ. Epigenetic mechanisms in memory and synaptic function. *Epigenomics* 3: 157–181, 2011.

475. Suomi SJ. Early determinants of behaviour: evidence from primate studies. *Br Med Bull* 53: 170–184, 1997.

476. Swanson JM, Entringer S, Buss C, Wadhwa PD. Developmental origins of health and disease: environmental exposures. *Semin Reprod Med* 27: 391–402, 2009.

477. Szuran TF, Pliska V, Pokorny J, Welzl H. Prenatal stress in rats: effects on plasma corticosterone, hippocampal glucocorticoid receptors, and maze performance. *Physiol Behav* 71: 353–362, 2000.

478. Tang YP, Wang H, Feng R, Kyin M, Tsien JZ. Differential effects of enrichment on learning and memory function in NR2B transgenic mice. *Neuropharmacology* 41: 779–790, 2001.

479. Tao X, Finkbeiner S, Arnold DB, Shaywitz AJ, Greenberg ME. Ca^{2+} influx regulates BDNF transcription by a CREB family transcription factor-dependent mechanism. *Neuron* 20: 709–726, 1998.

480. Tees RC, Buhrmann K, Hanley J. The effect of early experience on water maze spatial learning and memory in rats. *Dev Psychobiol* 23: 427–439, 1990.

481. Thoenen H. Neurotrophins and activity-dependent plasticity. *Prog Brain Res* 128: 183–191, 2000.

482. Thompson B, Mansouri B, Koski L, Hess RF. Brain plasticity in the adult: modulation of function in amblyopia with rTMS. *Curr Biol* 18: 1067–1071, 2008.

483. Thompson BL, Levitt P, Stanwood GD. Prenatal exposure to drugs: effects on brain development and implications for policy and education. *Nat Rev Neurosci* 10: 303–312, 2009.

484. Tian N, Copenhagen DR. Visual deprivation alters development of synaptic function in inner retina after eye opening. *Neuron* 32: 439–449, 2001.

485. Tian N, Copenhagen DR. Visual stimulation is required for refinement of ON and OFF pathways in postnatal retina. *Neuron* 39: 85–96, 2003.

486. Timney B, Mitchell DE, Giffin F. The development of vision in cats after extended periods of dark-rearing. *Exp Brain Res* 31: 547–560, 1978.

487. Tognini P, Manno I, Bonaccorsi J, Cenni MC, Sale A, Maffei L. Environmental enrichment promotes plasticity and visual acuity recovery in adult monocular amblyopic rats. *PLoS One* 7: e34815, 2012.

488. Torasdotter M, Metsis M, Henriksson BG, Winblad B, Mohammed AH. Environmental enrichment results in higher levels of nerve growth factor mRNA in the rat visual cortex and hippocampus. *Behav Brain Res* 93: 83–90, 1998.

489. Torasdotter M, Metsis M, Henriksson BG, Winblad B, Mohammed AH. Expression of neurotrophin-3 mRNA in the rat visual cortex and hippocampus is influenced by environmental conditions. *Neurosci Lett* 218: 107–110, 1996.

490. Tottenham N, Hare TA, Quinn BT, McCarry TW, Nurse M, Gilhooly T, Millner A, Galvan A, Davidson MC, Eigsti IM, Thomas KM, Freed PJ, Booma ES, Gunnar MR, Altemus M, Aronson J, Casey BJ. Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. *Dev Sci* 13: 46–61, 2010.

491. Trejo JL, Carro E, Torres-Aleman I. Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. *J Neurosci* 21: 1628–1634, 2001.

492. Tropea D, Van Wart A, Sur M. Molecular mechanisms of experience-dependent plasticity in visual cortex. *Philos Trans R Soc Lond B Biol Sci* 364: 341–355, 2009.

493. Turner AM, Greenough WT. Differential rearing effects on rat visual cortex synapses. I. Synaptic and neuronal density and synapses per neuron. *Brain Res* 329: 195–203, 1985.

494. Turner CA, Lewis MH, King MA. Environmental enrichment: effects on stereotyped behavior and dendritic morphology. *Dev Psychobiol* 43: 20–27, 2003.

495. Tyas SL, Salazar JC, Snowdon DA, Desrosiers MF, Riley KP, Mendiondo MS, Kryscio RJ. Transitions to mild cognitive impairments, dementia, and death: findings from the Nun Study. *Am J Epidemiol* 165: 1231–1238, 2007.

496. Tyas SL, Snowdon DA, Desrosiers MF, Riley KP, Markesbery WR. Healthy ageing in the Nun Study: definition and neuropathologic correlates. *Age Ageing* 36: 650–655, 2007.

497. Unterberger A, Szyf M, Nathanielsz PW, Cox LA. Organ and gestational age effects of maternal nutrient restriction on global methylation in fetal baboons. *J Med Primatol* 38: 219–227, 2009.

498. Valenzuela M, Sachdev P. Can cognitive exercise prevent the onset of dementia? Systematic review of randomized clinical trials with longitudinal follow-up. *Am J Geriatr Psychiatry* 17: 179–187, 2009.

499. Valenzuela MJ, Breakspear M, Sachdev P. Complex mental activity and the aging brain: molecular, cellular and cortical network mechanisms. *Brain Res Rev* 56: 198–213, 2007.

500. Valenzuela MJ, Sachdev P. Brain reserve and cognitive decline: a non-parametric systematic review. *Psychol Med* 36: 1065–1073, 2006.

501. Valenzuela MJ, Sachdev P. Brain reserve and dementia: a systematic review. *Psychol Med* 36: 441–454, 2006.

502. Valenzuela MJ, Sachdev P, Wen W, Chen X, Brodaty H. Lifespan mental activity predicts diminished rate of hippocampal atrophy. *PLoS One* 3: e2598, 2008.

503. Van Dellen A, Blakemore C, Deacon R, York D, Hannan AJ. Delaying the onset of Huntington's in mice. *Nature* 404: 721–722, 2000.

504. Van Hasselt FN, Cornelisse S, Zhang TY, Meaney MJ, Velzing EH, Krugers HJ, Joels M. Adult hippocampal glucocorticoid receptor expression and dentate synaptic plasticity correlate with maternal care received by individuals early in life. *Hippocampus* 22: 255–266, 2012.

505. Van Oers HJ, de Kloet ER, Li C, Levine S. The ontogeny of glucocorticoid negative feedback: influence of maternal deprivation. *Endocrinology* 139: 2838–2846, 1998.

506. Van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci USA* 96: 13427–13431, 1999.

507. Van Praag H, Kempermann G, Gage FH. Neural consequences of environmental enrichment. *Nat Rev Neurosci* 1: 191–198, 2000.

508. Van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci* 2: 266–270, 1999.

509. Van Praag H, Shubert T, Zhao C, Gage FH. Exercise enhances learning and hippocampal neurogenesis in aged mice. *J Neurosci* 25: 8680–8685, 2005.

510. Venable N, Fernandez V, Diaz E, Pinto-Hamuy T. Effects of preweaning environmental enrichment on basilar dendrites of pyramidal neurons in occipital cortex: a Golgi study. *Brain Res* 49: 140–144, 1989.

511. Vereecken EP, Brabant P. Prognosis for vision in amblyopia after the loss of the good eye. *Arch Ophthalmol* 102: 220–224, 1984.

512. Vickers A, Ohlsson A, Lacy JB, Horsley A. Massage for promoting growth and development of preterm and/or low birth-weight infants. *Cochrane Database Syst Rev* CD000390, 2004.

513. Villeda SA, Luo J, Mosher KI, Zou B, Britschgi M, Bieri G, Stan TM, Fainberg N, Ding Z, Eggel A, Lucin KM, Czirr E, Park JS, Couillard-Despres S, Aigner L, Li G, Peskind ER, Kaye JA, Quinn JF, Galasko DR, Xie XS, Rando TA, Wyss-Coray T. The ageing systemic milieu negatively regulates neurogenesis and cognitive function. *Nature* 477: 90–94, 2011.

514. Walsh RN, Budtz-Olsen OE, Penny JE, Cummins RA. The effects of environmental complexity on the histology of the rat hippocampus. *J Comp Neurol* 137: 361–366, 1969.

515. Walsh RN, Cummins RA. Changes in hippocampal neuronal nuclei in response to environmental stimulation. *Int J Neurosci* 9: 209–212, 1979.

516. Ward AJ. Prenatal stress and childhood psychopathology. *Child Psychiatry Hum Dev* 22: 97–110, 1991.

517. Weaver IC. Epigenetic programming by maternal behavior and pharmacological intervention. Nature versus nurture: let's call the whole thing off. *Epigenetics* 2: 22–28, 2007.

518. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ. Epigenetic programming by maternal behavior. *Nat Neurosci* 7: 847–854, 2004.

519. Weaver IC, Meaney MJ, Szyf M. Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. *Proc Natl Acad Sci USA* 103: 3480–3485, 2006.

520. Weinstock M. The long-term behavioural consequences of prenatal stress. *Neurosci Biobehav Rev* 32: 1073–1086, 2008.

521. West MJ, Coleman PD, Flood DG, Troncoso JC. Differences in the pattern of hippocampal neuronal loss in normal ageing and Alzheimer's disease. *Lancet* 344: 769–772, 1994.

522. Westenbroek C, Den Boer JA, Veenhuis M, Ter Horst GJ. Chronic stress and social housing differentially affect neurogenesis in male and female rats. *Brain Res Bull* 64: 303–308, 2004.

523. Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F. Physical activity, including walking, and cognitive function in older women. *JAMA* 292: 1454–1461, 2004.

524. Whitlock JR, Heynen AJ, Shuler MG, Bear MF. Learning induces long-term potentiation in the hippocampus. *Science* 313: 1093–1097, 2006.

525. Wiesel TN, Hubel DH. Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. *J Neurophysiol* 28: 1029–1040, 1965.

526. Wiesel TN, Hubel DH. Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J Neurophysiol* 26: 1003–1017, 1963.

527. Williams BM, Luo Y, Ward C, Redd K, Gibson R, Kuczaj SA, McCoy JG. Environmental enrichment: effects on spatial memory and hippocampal CREB immunoreactivity. *Physiol Behav* 73: 649–658, 2001.

528. Williamson JD, Espeland M, Kritchevsky SB, Newman AB, King AC, Pahor M, Guralnik JM, Pruitt LA, Miller ME. Changes in cognitive function in a randomized trial of physical activity: results of the lifestyle interventions and independence for elders pilot study. *J Gerontol A Biol Sci Med Sci* 64: 688–694, 2009.

529. Wilson DA, Willner J, Kurz EM, Nadel L. Early handling increases hippocampal long-term potentiation in young rats. *Behav Brain Res* 21: 223–227, 1986.

530. Wilson ME. Adult amblyopia reversed by contralateral cataract formation. *J Pediatr Ophthalmol Strabismus* 29: 100–102, 1992.

531. Wilson RS, Bennett DA, Bienias JL, Aggarwal NT, Mendes De Leon CF, Morris MC, Schneider JA, Evans DA. Cognitive activity and incident AD in a population-based sample of older persons. *Neurology* 59: 1910–1914, 2002.

532. Wingfield A, Grossman M. Language and the aging brain: patterns of neural compensation revealed by functional brain imaging. *J Neurophysiol* 96: 2830–2839, 2006.

533. Wolfer DP, Litvin O, Morf S, Nitsch RM, Lipp HP, Wurbel H. Laboratory animal welfare: cage enrichment and mouse behaviour. *Nature* 432: 821–822, 2004.

534. Woodard JL, Sugarman MA, Nielson KA, Smith JC, Seidenberg M, Durgerian S, Butts A, Hantke N, Lancaster M, Matthews MA, Rao SM. Lifestyle and genetic contributions to cognitive decline and hippocampal structure and function in healthy aging. *Curr Alzheimer Res* 9: 436–446, 2012.

535. Wu C, Hunter DG. Amblyopia: diagnostic and therapeutic options. *Am J Ophthalmol* 141: 175–184, 2006.

536. Wyrwoll CS, Holmes MC. Prenatal excess glucocorticoid exposure and adult affective disorders: a role for serotonergic and catecholamine pathways. *Neuroendocrinology* 95: 47–55, 2012.

537. Yaffe K, Fiocco AJ, Lindquist K, Vittinghoff E, Simonsick EM, Newman AB, Satterfield S, Rosano C, Rubin SM, Ayonayon HN, Harris TB. Predictors of maintaining cognitive function in older adults: the Health ABC study. *Neurology* 72: 2029–2035, 2009.

538. Yamada M, Kasagi F, Sasaki H, Masunari N, Mimori Y, Suzuki G. Association between dementia and midlife risk factors: the Radiation Effects Research Foundation Adult Health Study. *J Am Geriatr Soc* 51: 410–414, 2003.

539. Yeh CM, Huang CC, Hsu KS. Prenatal stress alters hippocampal synaptic plasticity in young rat offspring through preventing the proteolytic conversion of pro-brain-derived neurotrophic factor (BDNF) to mature BDNF. *J Physiol* 590: 991–1010, 2012.

540. Yoshii A, Constantine-Paton M. Postsynaptic BDNF-TrkB signaling in synapse maturation, plasticity, and disease. *Dev Neurobiol* 70: 304–322, 2010.

541. Young D, Lawlor PA, Leone P, Dragunow M, During MJ. Environmental enrichment inhibits spontaneous apoptosis, prevents seizures and is neuroprotective. *Nat Med* 5: 448–453, 1999.

542. Young JI, Hong EP, Castle JC, Crespo-Barreto J, Bowman AB, Rose MF, Kang D, Richman R, Johnson JM, Berget S, Zoghbi HY. Regulation of RNA splicing by the methylation-dependent transcriptional repressor methyl-CpG binding protein 2. *Proc Natl Acad Sci USA* 102: 17551–17558, 2005.

543. Zeanah CH, Nelson CA, Fox NA, Smyke AT, Marshall P, Parker SW, Koga S. Designing research to study the effects of institutionalization on brain and behavioral development: the Bucharest Early Intervention Project. *Dev Psychopathol* 15: 885–907, 2003.

544. Zhang H, Cai R, Zhang J, Pan Y, Sun X. Environmental enrichment enhances directional selectivity of primary auditory cortical neurons in rats. *Neurosci Lett* 463: 162–165, 2009.