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Review

Nurturing brain plasticity: impact of environmental enrichment

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Environmental enrichment (EE) is known to profoundly affect the central nervous system (CNS) at the functional, anatomical and molecular level, both during the critical period and during adulthood. Recent studies focusing on the visual system have shown that these effects are associated with the recruitment of previously unsuspected neural plasticity processes. At early stages of brain development, EE triggers a marked acceleration in the maturation of the visual system, with maternal behaviour acting as a fundamental mediator of the enriched experience in both the foetus and the newborn. In adult brain, EE enhances plasticity in the cerebral cortex, allowing the recovery of visual functions in amblyopic animals. The molecular substrate of the effects of EE on brain plasticity is multi-factorial, with reduced intracerebral inhibition, enhanced neurotrophin expression and epigenetic changes at the level of chromatin structure. These findings shed new light on the potential of EE as a non-invasive strategy to ameliorate deficits in the development of the CNS and to treat neurological disorders.
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Adult brain architecture is the result of a complex interaction between genetic developmental programmes and experience-driven plasticity processes.[1,2] A large number of studies demonstrated the existence of time windows in early postnatal life, named critical periods (CPs), during which neural circuits display a heightened sensitivity to acquire instructive and adaptive signals from the external environment. Various brain regions subserving major behavioural functions (e.g., sensory perception, motor control and language) have CPs that occur at different times and are activated and regulated by distinct mechanisms.[3,4]

The primary visual cortex (V1) is a paradigmatic model for studying experience-dependent plasticity. Although the maturation of the visual system starts before eye opening and the initial targeting of neural connections is subjected to either genetic programmes or spontaneous activity, a proper development of the visual system requires sensory experience.[5,6] A total absence of sensory input leads to a delay in the functional and anatomical maturation of the visual cortex, which appears immature far beyond the end of the critical period. Adult animals reared in darkness from birth (dark rearing, DR) display serious physiological deficits in their visual cortex, including reduced orientation and direction tuning, lower cell responsiveness, larger receptive field sizes, altered spontaneous activity, immature ocular dominance (OD) distribution and lower visual acuity (VA).[7–10]

Ocular dominance plasticity refers to the rapid change in visual cortex physiology resulting from unbalanced inputs from the two eyes. Hubel and Wiesel[11,12] first reported in kittens that reducing input from one eye by lid suture (monocular deprivation, MD) during development dramatically affects the binocularity of V1, leading to a loss of cortical responses to that eye and an increase in the number of neurons preferentially driven by the open eye. As a direct consequence, the deprived eye becomes amblyopic: its VA is strongly reduced and its contrast sensitivity is blunted. The effects of MD and the existence of a CP have been subsequently described in other species of mammals as well, including primates,[13] rabbits,[14] hamsters,[15] rats,[10] mice[16] and ferrets.[17]

In parallel to experiments based on protocols of reduced or altered sensory experience, relevant progress in understanding the influence of environmental experience on the development, refinement and maintenance of appropriate neural

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Abbreviations: 5-HT, 5-hydroxytryptamine; A1, primary auditory cortex; AD, Alzheimer disease; NGF, nerve growth factor; APP, amyloid precursor protein; AMPA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; APOE, apolipoprotein E; BACE, β-site APP-cleaving enzyme; BDNF, brain-derived neurotrophic factor; BFCN, basal forebrain cholinergic neurons; CaMKII, Ca2 + /calmodulin-dependent protein kinase II; RT-PCR, real-time polymerase chain reaction; CNS, central nervous system; CP, critical period; CRE, cAMP response element; CREB, cAMP response element binding; CSPG, chondroitin-sulfate proteoglycans; DR, dark rearing; DS, Down syndrome; Chr, chromosome; EE, environmental enrichment; GABA, γ-aminobutyric acid; GAD65, glutamic acid decarboxylase 65; IGF-I, insulin-like growth factor I; LTP, long-term potentiation; MD, monocular deprivation; NMDA, N-methyl-D-aspartic acid; EEG, electroencephalogram; NT-3, neurotrophin-3; OD, ocular dominance; VA, visual acuity; PNN, perineuronal net; PS1/2, presenilin 1/2; ReS, Rett sindrome; MeCP2, methyl-CpG binding protein; RGC, retinal ganglion cell; SOD1/2, superoxide dismutase 1/2; V1, primary visual cortex; VEGF, vascular endothelial growth factor; VEP, visual evoked potential; WM-LTP, white-matter long-term potentiation
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Figure 1 Environmental enrichment (EE) is a manipulation of the standard laboratory conditions that modify the quality and intensity of environmental stimulation, reaching an optimization of the rearing environment. The goal of EE is to provide animals with increased levels of multisensory stimulation, physical activity and social interactions, and by eliciting spontaneous explorative behaviours. Drawing by M. Marchi

connections has been made possible by paradigms specifically devoted to increasing the quality and intensity of environmental stimulation, such as environmental enrichment (EE). EE is defined as 'a combination of complex inanimate and social stimulation'.[18] Enriched animals are reared in large groups and housed in widely stimulating environments in which a variety of differently shaped objects are present and changed frequently. The goal of EE is to improve the animals' quality of life by providing them with a combination of multisensory/cognitive stimulation, increased physical activity, enhanced social interactions and by eliciting natural explorative behaviours (Figure 1). Hence, in contrast to the approaches based on sensory deprivation, EE is a gain-of-function paradigm allowing the study of the influence elicited by increased levels of environmental stimulation on brain development and plasticity.

Environmental enrichment exerts profound effects on the adult central nervous system (CNS). A large number of studies highlighted the fact that EE modifies the behaviour of animals, leading to a sensitive improvement in complex cognitive functions, particularly learning and memory,[19] and positively affecting the animal's emotional and stress reactivity.[20] Rodents living in EE conditions display increased levels of hippocampal long-term potentiation (LTP), a physiological model of synaptic plasticity related to learning and memory.[21] This functional improvement is accompanied by prominent changes at the anatomical level, with robust increments in cortical thickness and weight and modifications of neuronal morphology, in terms of increased dendritic arborization, number of dendritic spines, synaptic density and postsynaptic thickening, occurring in several regions of the brain, particularly in the occipital cortex and hippocampus.[22] Moreover, exposure to EE increases hippocampal neurogenesis and the integration of newly born cells into functional circuits.[21] At the molecular level, EE causes a significant change in the expression of a large set of genes involved in neuronal structure, excitability, synaptic transmission and plasticity,[23] modulating the synthesis and secretion of neurotrophic factors throughout the brain and affecting the cholinergic, serotoninergic and noradrenergic systems.[24–27]

Although EE research has been mostly focused on rodents, similar effects have been reported in several species of mammals (gerbils, ground squirrels, rabbits, cats and primates).[28–32]

Influence of EE on Brain Developmental Plasticity

Despite the large body of evidence with regard to the effects of EE on the adult brain, until recently, the influence of EE on the developmental physiology and plasticity of the CNS has remained only scarcely investigated. In the past few years, this gap has been considerably filled with a series of studies focusing on the visual system as a paradigmatic model. The most relevant result was the demonstration that EE from birth induces a marked acceleration in the maturation of VA, an effect consistently reported in mice and rats using both electrophysiological and behavioural methods.[33–36] The acceleration effect is quite strong, yielding a 1-week advance in the time course of VA maturation with respect to control animals. This functional outcome is accompanied by a precocious decline in the possibility of inducing LTP of layer II–III field potentials after theta-burst stimulation of the white matter (WM-LTP) in the visual cortex,[34] a well-established *in vitro* model of developmental plasticity.[37] EE also promotes visual system maturation in the absence of visual experience, with DR rats maintained in EE conditions showing a normal VA development and closure of the CP for OD plasticity.[38] This indicates that non-visual stimulation counteracts the effects exerted by a complete lack of visual experience from birth. In the auditory system, pre-weaning EE improves spatial localization abilities and enhances directional sensitivity of A1 neurons,[39] whereas it remains unexplored whether exposure to EE conditions induces compensation for the delay in A1 maturation prompted by white noise rearing.

It is worth noting that rearing animals in EE during their early phases of life leads to a functional phenotype very similar to that previously reported in transgenic mice overexpressing BDNF in the forebrain.[40,41] Indeed, mice raised in EE show increased levels of the BDNF protein in their visual cortex at P7,[34,35] revealing the fact that neurotrophin BDNF is one of the crucial factors that underlie EE effects on V1 maturation. In both BDNF overexpressing mice and EE pups, higher BDNF levels were also shown to trigger the maturation of the inhibitory GABAergic system, which, by affecting receptive field development and synaptic plasticity, could determine both the accelerated maturation of VA and the decline of cortical plasticity.[34,35,40]

Another molecular factor involved in mediating EE effects on visual system development is IGF-I.[42] IGF-I expression is higher at P18 in the visual cortex of EE rats compared with non-EE rats. Moreover, exogenous IGF-I supply mimics, whereas blocking IGF-I action prevents the EE effects on VA maturation. The authors observed that inhibitory interneurons respond to IGF-1 with a GAD65 increase in their synaptic terminals, suggesting that a possible explanation for the effects of IGF-I on VA development could be an action on the inhibitory GABAergic system.[42]

BDNF and IGF-I signalling may eventually converge on the activation of intracellular pathways, leading to the phosphorylation of the transcription factor CREB. The wave of CREB/CRE-mediated gene expression in the visual cortex is

accelerated in EE mice, and chronic injections of non-EE animals with rolipram, a pharmacological treatment increasing the phosphorylation of CREB, partially mimic the EE outcome on VA maturation.[34] Thus, activation of the CREB/CRE transcription pathway may be one crucial mediator of the EE effects on visual system development.

Retina development is also affected by high levels of environmental stimulation. It has been recently reported that DR induces alterations in both the anatomical stratifications of retinal ganglion cells (RGCs) and the visual responsiveness of inner retinal neurons.[43,44] EE accelerates the segregation of RGC dendrites into ON and OFF sublaminae,[36] as well as the rise of retinal acuity during development, even in animals exposed to differential rearing before eye opening, for the first 10 days of life.[45] IGF-I and BDNF are key molecular factors in these processes: retinal levels of both proteins are precociously increased in the RGC layer of developing EE rats, and blocking either IGF-I or BDNF action in EE animals counteracts the faster retinal maturation.[36,45,46] BDNF turned out to be a downstream target of IGF-I.[46]

Strikingly, the maturation of the nervous system is sensitive to environmental stimulation during prenatal life as well. Recent data by Sale *et al*.[47] demonstrated that exposing pregnant females to EE (maternal enrichment) profoundly affects the development of the retina in embryos, leading to an acceleration of structural processes critical for retinal maturation, such as the migration of neural progenitors and the time course of naturally occurring cell death in the RGC layer. Interestingly, a key factor in the effects of maternal enrichment on retinal morphology and function is IGF-I. Anatomical modifications are indeed accompanied by a marked increase in IGF-I levels in the retinas of EE pups and in maternal milk. Furthermore, IGF-I infusion during late pregnancy is sufficient to induce, in non-EE animals, all the reported changes elicited by EE in foetuses, whereas neutralization of IGF-I in EE mothers prevents the action of maternal enrichment on retinal development.[47]

The influence of increased maternal stimulation during pregnancy is not only restricted to the visual system. Voluntary wheel running of pregnant mice leads to a twofold increase in hippocampal precursor-cell proliferation in their pups.[48] Maternal physical activity in the form of swimming during pregnancy has also been shown to increase hippocampal BDNF mRNA expression in the offspring leading to improved short-term memory abilities.[49]

Maternal Care, Tactile Stimulation and Visual System Development

The aforementioned studies demonstrate that, far from being rigidly determined by genetic programmes, CNS development is already responsive to the environment at very early stages. The first two weeks of rodent life are characterized by the prevalent absence of a direct interaction between the pup and the external environment, with newborns spending their whole time in the nest, where the mother is the most important source of sensory experience.[50] It was soon realized that differences in maternal behaviour between EE and non-EE conditions could be a fundamental factor triggering the earliest effects of EE on visual system development. This issue has been directly addressed by a detailed quantitative study of maternal behaviour in different environmental conditions, which led to the first demonstration that EE pups receive higher levels of maternal care compared with standard-reared pups.[35] More specifically, EE animals experience a continuous physical contact because of the presence of adult females in the nest and are also provided with increased levels of licking and grooming (Figure 2a). The amount of maternal care received by the developing pup influences hippocampal structure and function, affects molecular factors crucial for plasticity such as BDNF and NMDA receptors and leaves long-lasting epigenetic marks in the offspring's physiology and behaviour.[50–53]

Very recently, a protocol of daily artificial tactile stimulation has been used in the rat as a strategy to promote visual system development.[54] The authors reported that a combination of gently stroking and massaging is highly effective in accelerating the maturation of physiological visual functions, in particular of VA (Figure 2b). Interestingly, tactile stimulation increases IGF-I levels in the visual cortex at P18, as also observed in EE animals, and blocking IGF-I action prevents the effects of massage on VA development.[54] Tactile stimulation also compensates for inadequate maternal care: the negative effects produced by repeated episodes of maternal separation or by prenatal stress on pup growth, hormone secretion, hypothalamus–pituitary–adrenal axis and BDNF expression are all rescued by artificial massage applied to pups in order to mimic maternal behaviour.[55–57] Altogether, these results provide a remarkable example of cross-modal plasticity by which an increased input in a single modality reverberates as a driving force for the whole brain.

Strikingly, Guzzetta *et al.*[54] demonstrated that massage therapy also accelerates brain development in healthy preterm infants (gestational age between 30 and 33 weeks). The authors found that massaged infants exhibit an earlier shortening of the interbust intervals in the EEG, a robust index of the developmental stage of the brain, a significantly greater reduction in the latency of flash VEPs and an increase in behavioural VA outlasting the end of treatment (Figure 2c). In parallel to the results found in the animal model, massaged infants showed increased levels of plasma IGF-I, confirming that this molecule is crucially involved in mediating the effects of an enhanced sensory stimulation in the brain.[54] This result is supported by the finding that, in preterm infants, tactile stimulation causes an increase in growth hormone production[55] and an enhancement of serum IGF-I.[58] Finally, very recent papers have shown that IGF-I and IGF-I binding protein 3 (IGFBP3) could be protective against proliferative retinopathy of prematurity, a severe and relatively frequent visual disorder in preterm infants.[59,60] The paper by Guzzetta *et al*.[54] underlines the role of environmental stimulation as a crucial factor for early postnatal development in humans. Massage therapy could be a good implementation of normal intensive treatment reserved for preterm babies aimed at more efficaciously counteracting the onset of neurological pathologies associated with a precocious delivery.

Rejuvenating the Adult Brain

A classical dogma in neuroscience is that brain plasticity undergoes a dramatic decline with age. Significant effort is being made in multiple laboratories to develop new strategies

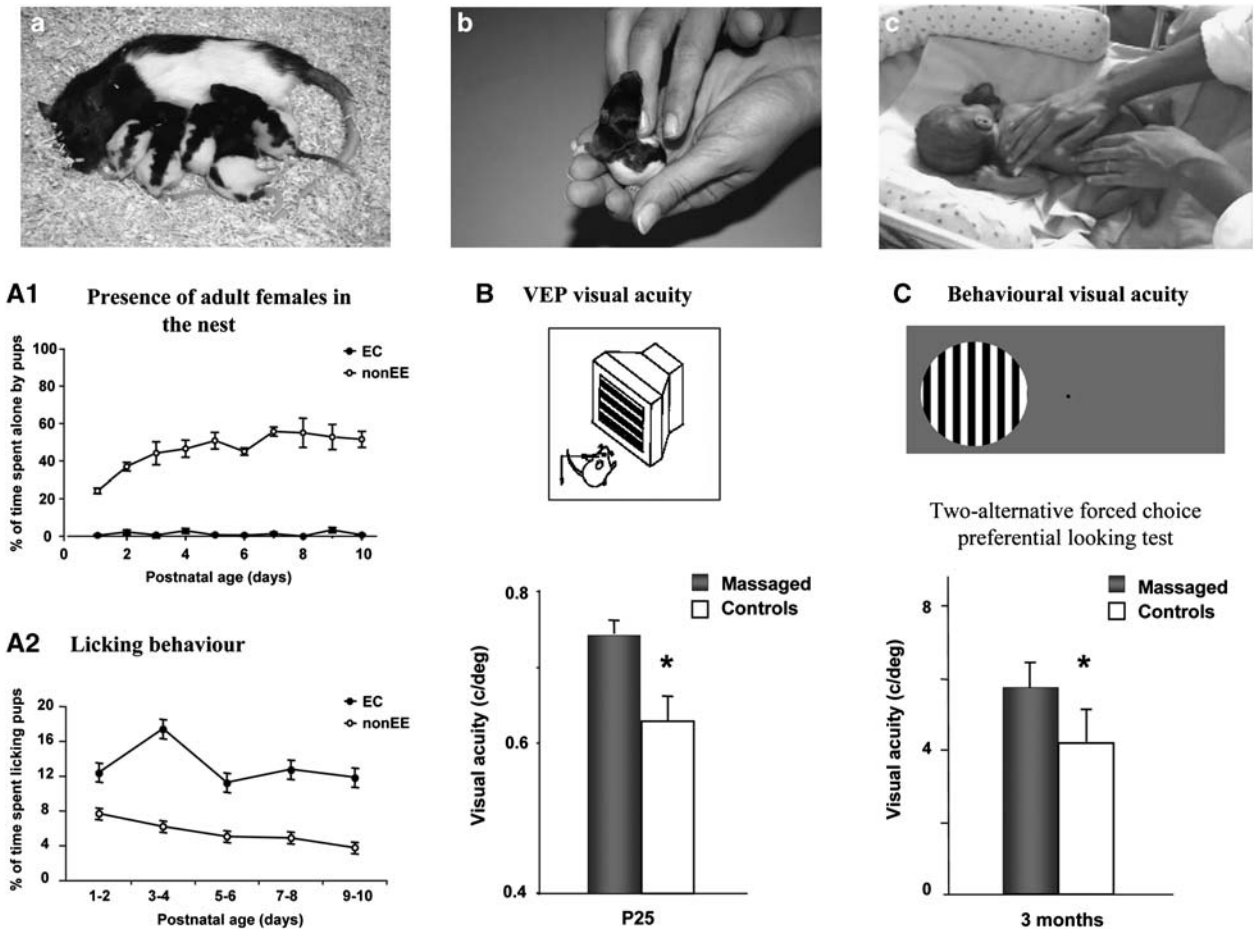

Figure 2 (**a**) Enriched pups experience higher levels of maternal care compared with standard-reared pups. (A1) The frequency of 'pups alone in the nest' recordings during the first 10 days postpartum in non-environmental enrichment (EE) (white) and EE (black) animals. Two-way RM ANOVA revealed a significant effect of age and housing condition ($P<0.001$) and a significant interaction between age and housing condition ($P<0.001$). SNK *post hoc* analysis revealed that groups differ statistically ($P<0.05$). Vertical bars are S.E.M. (A2) Frequency of 'licking' recordings during the first 10 days postpartum in non-EE (white) and EE (black) animals. Two-way RM ANOVA revealed a significant effect of age and housing condition ($P<0.001$) and a significant interaction between age and housing condition ($P<0.05$). SNK *post hoc* analysis revealed that groups were statistically different ($P<0.05$). Vertical bars are S.E.M. Graphs have been modified from Sale *et al.*[35] (**b**) Massage in rat pups accelerates visual acuity maturation. The massage protocol combined gently stroking and massaging to mimic maternal care. Each animal received 5 min of tactile stimulation thrice a day: 2 min with a wet soft paintbrush on their back, head, limbs and abdomen to mimic licking; 1.5 min massage with finger tips on both sides of their back combined with passive gentle movement of their limbs; 1.5 min with a soft toothbrush on the back and abdomen to mimic grooming. (B1) Mean visual acuity determined at P25 by means of VEPs recorded from the primary visual cortex for massaged (grey) and control rats (white). The massage group significantly differs from the control group (one-way ANOVA, factor treatment significant, $P<0.05$, *post hoc* Holm–Sidak method). An asterisk denotes significant difference. Vertical bars are S.E.M. Graph has been modified from Guzzetta *et al.*[54] (**c**) Maturation of the visual system is accelerated in massaged preterm infants. Massage therapy was begun on day 10 (± 1) after birth. Sessions were performed thrice a day for two blocks of 5 days each, separated by a 2-day interval. Each treatment session consisted of 10 min of tactile stimulation, followed by 5 min of kinaesthetic stimulation. During tactile stimulation, the infant was placed prone and was given moderate pressure stroking with the flats of the fingers of both hands. Head, neck, shoulders, buttocks and both legs and arms were stimulated. For the kinaesthetic phase, the infant was placed in a supine position. Passive flexion/extension movements of the limbs in sequence were applied. (C1) Behavioural visual acuity measured by means of the Vital-Durand Acuity Cards at 3 months corrected age. Visual acuity in massaged infants is significantly higher than in controls at 3 months ($P<0.05$, *t*-test). Normal value for term-born infants at 3 months is 3–5.2 c/deg. An asterisk denotes significant difference. Vertical bars are S.E.M. Graph has been modified from Guzzetta *et al.*[54]

aimed at enhancing CNS plasticity after the end of CP. In this fascinating field, the visual system emerges as the election test bed. Visual experience, indeed, can be easily controlled and the consequences of manipulations are readily measured at the anatomical, cellular and molecular level. From classic experiments in animal models to human clinical studies, it is well known that early abnormal visual experience owing to anisometropia (unequal refractive power in the two eyes), strabismus (abnormal alignment of one or both eyes), congenital cataract or, in animal models, MD results in a functional imbalance between the two eyes, leading to amblyopia, a widely diffused pathology (2–5% incidence in the human population) for which no suitable treatment is yet available in the adult.[61] Amblyopia causes a dramatic loss of VA in an apparently healthy eye, with a great deal of evidence showing that it also results in a broad range of other perceptual abnormalities, including deficits in stereopsis and contrast sensitivity.[62,63] Similarly, in animal models, the classic hallmarks of amblyopia are a permanent loss of VA in the affected eye and a pronounced OD shift of visual cortical neurons in favour of the normal eye.[64–68] Traditional amblyopia therapy consists of patching

or penalizing the preferred fellow eye, thus forcing the brain to use the visual input carried by the weaker amblyopic eye.[69]

Although it is widely accepted that the reinstatement of visual functions is possible only if corrective therapy is started early in development, recent studies in rodents have unmasked a previously unsuspected potential for promoting recovery well after the end of CP (for a recent review, see Spolidoro *et al.*[70]). EE turned out to be very effective for treating amblyopia in adulthood. A brief exposure (2–3 weeks) of adult amblyopic rats to EE has been demonstrated to promote a complete recovery of both VA and OD, an effect documented not only at the electrophysiological level but also by using behavioural assessments[71] (Figure 3a). Recovery of plasticity in EE rats is associated with a threefold reduction in the basal levels of GABA detected in the visual cortex by *in vivo* brain microdialysis. As a consequence of decreased cortical inhibition, EE dynamically regulates cortical synaptic plasticity as well, resulting in a recovery of the possibility to evoke WM-LTP in visual cortical slices,[71] a form of LTP that is normally occluded in adulthood as a result of the maturation of inhibitory circuits.[37,40] The reduction of inhibition has proved to be a crucial molecular mechanism underlying the enhancement of plasticity induced by EE (Figure 3b), because restoration of plasticity is completely prevented by benzodiazepine cortical infusion during the EE period.[71] The excitatory-inhibitory balance of cortical activity is well known to be crucially involved in regulating plasticity in the developing and adult brain.[40,72] Consistently, chronic fluoxetine administration, another manipulation that reactivates cortical plasticity in adulthood promoting a full reinstatement of OD plasticity in response to MD and the recovery of visual functions from amblyopia, reduces GABAergic transmission, and its effects are prevented by enhancing inhibition with diazepam.[73] There is also indirect evidence that the enhanced experience-dependent visual cortical plasticity driven by exposure of adult rats to complete darkness may also be related to a reduced expression of GABAA receptors relative to AMPA receptors, thus altering the balance between inhibition and excitation in the visual cortex.[74,75]

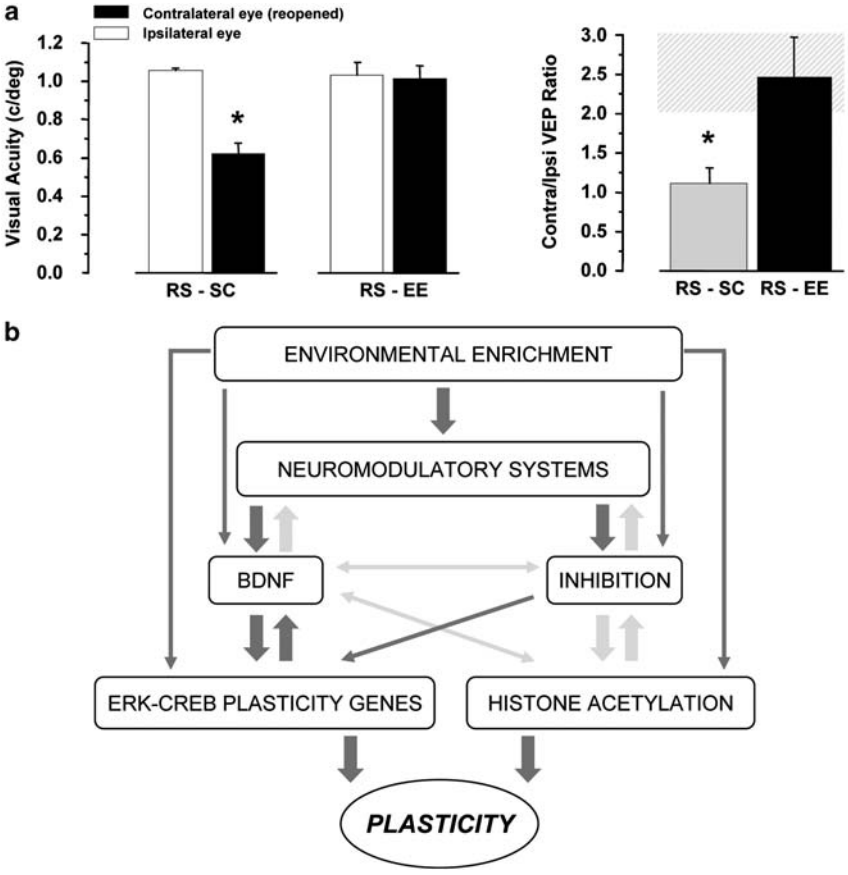

Figure 3 Experience-dependent reactivation of neural plasticity in the adult visual cortex. (**a**) EE in adulthood promotes visual acuity and binocularity recovery from amblyopia. Left: Behavioural and electrophysiological measurements of visual acuity of the two eyes revealed that the visual acuity of the amblyopic eye was significantly recovered in RS-EE (paired *t*-test, $P = 0.864$), but not in RS rats raised in standard conditions (SC) (paired *t*-test, $P < 0.05$). Right: The VEP ratio was statistically lower in RS-SC compared with RS-EE rats (*t*-test, $P < 0.05$), but did not differ between RS-EE and normal (not deprived) adult rats ($P = 0.907$). The hatched grey box represents the range of values for the VEP ratio in adult normal animals. Asterisks indicate statistical significance. Error bars represent S.E.M. Graphs have been modified from Sale *et al.*[71] (**b**) Schematic diagram showing key molecular events underlying restoration of plasticity in the adult visual system. We propose a model in which environmental stimulation could promote the strengthening of neuromodulatory transmission that triggers the decrease in GABA-mediated intracortical inhibition and, in parallel or in series, the enhancement of BDNF expression. Both the increase in overall cortical activity and BDNF intracellular signalling could in turn induce a transcriptional programme that leads to activation of other genes promoting plasticity, for instance through the ERK–CREB pathway. Furthermore, an influence on the epigenetic control of gene transcription has been suggested for EE. Dark grey arrows represent well-documented interactions between boxes; light grey arrows indicate likely interactions in the context of visual cortical plasticity, deserving further experimental characterization

The promising results obtained with EE in rodents provide new hope for clinical application to human patients, given the completely non-invasive nature of this approach. Strikingly, an increasing number of clinical studies have reported that repetitive visual training based on sensory enrichment procedures may represent a very useful approach for the treatment of amblyopia, providing substantial improvement in a variety of visual tasks[76–79] (for a review, see Polat[80] and Levi and Li[81]). One caveat to the therapeutic value of these visual practice procedures, however, is the narrow specificity of achievable improvement, which is typically limited to the selected trained stimulus, condition or task.[82] Only in a few tasks (Vernier acuity, contrast sensitivity and detection) did training lead, at least in some subjects, to a generalization of beneficial effects to other degraded visual functions, such as VA and stereoacuity.[81] Interestingly, it has been suggested that the balance between excitation and inhibition is also impaired during development in amblyopic human subjects and that cortical overinhibition could underlie the degradation of spatial vision abilities.[83–87]

The study of experimental models of amblyopia has the advantage of enabling researchers to uncover new molecular mechanisms underlying the therapeutic value of the used procedures. The reduction of cortical inhibition in the visual cortex of EE rats is paralleled by an increased expression of BDNF[71] (Figure 3b), a neurotrophic factor critical for experience-dependent plasticity.[40] Interestingly, it has been recently shown that intracortical administration of BDNF reactivates neural plasticity in the adult visual cortex[73] and that TrkB signalling is required for the recovery of deprived-eye responses subsequent to the reinstatement of binocular vision during development.[88] EE also leads to increased levels of histone acetylation in the hippocampus and neocortex.[89] A similar relationship between histone acetylation and EE effects could be present in the adult visual system (Figure 3b), in which pharmacological treatment with inhibitors of histone deacetylases restores OD plasticity.[90] Another way by which EE can regulate gene expression might be the activation of specific transcription factors. One possibility is that BDNF intracellular signalling stimulates CREB phosphorylation and activation,[91–93] which has a pivotal role in various forms of plasticity in the visual cortex[94–96] and other brain structures.[97] In line with this hypothesis, it has been shown that EE in adulthood increases immunoreactivity to CREB in the hippocampus as well[98] (Figure 3b).

Moving from the intracellular environment to the extracellular milieu, one interesting observation is that EE in amblyopic rats reduces the density of chondroitin-sulphate proteoglycan (CSPG) perineuronal nets (PNNs) in the visual cortex.[71] CSPGs exert a powerful repressive control on adult plasticity. This is demonstrated by pharmacological studies in which the removal of crucial components of PNNs from the mature extracellular matrix, by means of the enzyme chondroitinase ABC, reactivates OD plasticity in monocularly deprived adult rats and promotes recovery from the effects of early visual deprivation on VA and binocularity of cortical neurons.[99,100] These functional effects are accompanied by a recovery of dendritic-spine density, indicating that the removal of CSPGs favours remodelling of synaptic contacts onto visual-cortex pyramidal neurons.[100]

Thus, working with EE offers the opportunity to affect brain dysfunctions at multiple sites of action, either by allowing the replication of the successful outcome obtained with pharmacological treatment that is difficult to apply in humans or by indicating completely new ways of intervention.

The exact molecular modifications occurring upstream from the decrease in intracortical inhibition and the enhancement of BDNF expression observed in EE rats still need to be clarified. One appealing possibility is the involvement of neurotransmitter systems characterized by diffuse projections throughout the entire brain, which have been reported to profoundly affect plasticity in both the developing and adult brain.[73,101] First studies by Rosenzweig *et al*.[24,102] reported an increase in acetylcholinesterase activity, indicating an effect on the cholinergic system. Subsequent studies confirmed and extended this initial observation to other neurotransmitter systems, showing that EE increases noradrenaline concentration and strengthens the β-adrenoceptor signalling pathway in the cerebral cortex, cerebellum and brainstem,[27,103] and augments mRNA expression levels of serotonin 1A receptor and serotonin (5-HT) concentration in the cerebral cortex and hippocampus.[25,104,105] Interestingly, *in vitro* studies have repeatedly reported that 5-HT, acetylcholine, dopamine and, to a lesser extent, noradrenaline, suppress inhibition in several brain regions, including the visual cortex, possibly through a presynaptic mechanism mediated, respectively, by 5-$HT_{1/2}$, muscarinic D1 and the α-adrenergic receptor families.[106–113] Moreover, very recently, a modification of visual cortex pyramidal neuron responses to input signals depending on the behavioural state has been observed, related to a bidirectional modulation of somatic inhibition.[114] Equally, a vast number of studies have shown that neuromodulators, and in particular 5-HT, dramatically increase the expression of BDNF mRNA in the neocortex.[115–118] These facts, together with the recent finding that fluoxetine administration leads to a reduced GABAergic neurotransmission and an increased BDNF expression in the visual cortex of adult rats,[73] indicate that 5-HT might act as an effective trigger of EE effects on adult cortical plasticity (Figure 3b). Interestingly, the neuromodulatory systems are known to regulate the arousal state of the brain[101] and to modulate attentional processes.[119–121] A recent study in non-amblyopic subjects provides indirect support to the important role of visual attention in driving visual cortex plasticity, showing that normal-sighted people trained with action-based video games have robust improvements in basic visual functions.[122] The same effect was not observed after non-action video game playing (equally engaging and visually complex, but operating at a slower pace and not requiring precise visually guided actions), suggesting that allocation of attention is a fundamental component for the effectiveness of the training paradigm.[123,124]

Beyond the Sensory Cortex: EE Effects on Animal Models of Cognitive Impairment

The encouraging results obtained using EE as a tool to modulate the development of the CNS and as a strategy to reopen plasticity windows in the adult have shown that it is possible to control processes crucial for brain function in a

totally non-invasive manner. An important line of research deals with the potential therapeutic effects of EE in experimental models of nervous system injuries and disorders (for a comprehensive review, see Will *et al.*[125] and Nithianantharajah and Hannan[126]). Given that the action of EE on brain plasticity is multi-factorial, reducing intracerebral inhibition,[71] increasing histone acetylation[89] and enhancing neurotrophin expression,[26] it may be particularly efficacious in delaying the progression and/or in ameliorating the symptoms of those neurological disorders in which neuronal plasticity is compromised due to alterations in some or all of these processes. Here, we focus on Rett's syndrome, Down's syndrome and Alzheimer's disease.

Rett's syndrome. Rett's syndrome (ReS) is a progressive disorder of CNS development that predominantly affects the female population in early childhood. After a period of apparently normal development, the onset of developmental stasis and rapid deterioration occurs at 6–18 months of age, resulting in a complex neurological and neurobehavioural phenotype with mild-to-moderate mental retardation and severe dysfunction in motor coordination skills.[127] ReS has been related to loss-of-function mutations in the X-linked gene encoding the methyl-CpG-binding protein (MeCP2) involved in the regulation of epigenetic mechanisms of gene expression.[128] MeCP2 is a multi-functional protein having a key function in transcriptional silencing and activation[129] and in the modulation of RNA splicing.[130]

Mice carrying conditional deletion or neuron-specific expression of mutated MeCP2 forms provide a very good model in which to examine behavioural and molecular mechanisms of ReS.[131,132] These transgenic mice exhibit abnormalities in motor coordination, social interaction and cognitive abilities, with hemizygous males displaying the most severe phenotype.[131–134] Electrophysiological studies from MeCP2 transgenic mice reported reduced neuronal activity in cortical[135] and hippocampal[136] neurons, suggesting that a shift in the balance between inhibition and excitation could be responsible for rapid motor, behavioural and cognitive regression typical of ReS.[137] MeCP2-deficient mice have attenuated ability to express LTP in the hippocampus[136,138] and in the motor and somatosensory cortex.[138]

Importantly, the gene encoding BDNF is under MeCP2 regulation,[139] and the progression of symptoms in MeCP2-deficient mice seems to be correlated with gradually decreasing levels of circulating BDNF.[140] Given that BDNF expression depends on neuronal activity, the reduced neuronal excitability caused by MeCP2 insufficiency could lead to a decreased BDNF protein level.[140] BDNF overexpression in MeCP2 mutant mice is able to compensates the deficits at both the behavioural and electrophysiological level.[140] This implies that neurons deficient in functional MeCP2 retain the capacity to recover when appropriate neurotrophic signalling is re-established. Similarly, motor coordination and cognitive deficits in MeCP2 mutant mice are also reversed by EE.[141,142] The fundamental mechanisms through which EE exerts its beneficial effects, that is, increased trophic factor expression, decreased inhibition and increased activity-dependent hystone acetylation,[143] are all involved in the pathogenesis of ReS, thus indicating a strong rationale for the use of EE to treat ReS cognitive deficit. Accordingly, BDNF is increased in the cerebellum of MeCP2 mutant mice exposed to EE[141] and systemic infusion of IGF-I partially reverts their ReS-like symptoms.[144]

Down's syndrome. Down's syndrome (DS) is caused by triplication of chromosome 21 (Chr21) and is the most diffused genetic cause of mental retardation. People with DS have marked cognitive deficits, with reduced IQ and learning and memory performances.[145] During recent years, several murine models of DS have been generated, carrying triplications of different segments of Chr16, which has a high degree of synteny with human Chr21.[146,147] The most intensively studied mouse model of DS is the Ts65Dn line,[148] which summarizes the main hallmarks of the DS phenotype, including characteristic craniofacial abnormalities, impaired spatial and non-spatial learning abilities and attention deficits.[149–154] At the cellular level, Ts65Dn mice have a reduced number of hippocampal and cerebellar neurons,[155,156] impaired neurogenesis in the dentate gyrus of the hippocampus in both young and aged adults[157,158] and a prominent reduction in dendritic branching in several brain regions, accompanied by alterations in spine size and shape.[159] It is noteworthy that DS is also associated with reduced hippocampal neurogenesis[160] and volume[161] in humans. Adult Ts65Dn mice show age-dependent degeneration of basal forebrain cholinergic neurons (BFCNs),[162] the most characteristic neuropathological correlate of the late cognitive decline observed in Alzheimer's disease (AD). Virtually all persons born with DS develop AD if they live into their fourth decade of life.[163,164] There is evidence that degeneration of BFCNs in Ts65Dn mice is related to a marked decrease in the NGF retrograde transport from the hippocampus to the basal forebrain.[165,166] Intracerebroventricular NGF infusion reverses BFCN morphological abnormalities, restoring the deficit in cholinergic innervation.[165] BDNF signalling in Ts65Dn mice is also disrupted. In the frontal cortex, lower levels of BDNF with respect to diploid animals are found and negatively correlated with the progressive deterioration of working memory performance.[167]

A major functional synaptic defect detectable in Ts65Dn mice is the failure to induce LTP in the hippocampus.[168–171] This deficit has been attributed to excessive inhibition,[171] a hypothesis recently confirmed by Fernandez *et al.*,[172] which showed that the spatial learning disabilities observed in Ts65Dn mice are rescued by administration of non-competitive antagonists of GABAA receptors. The impairment in synaptic plasticity is linked to marked morphological changes in the structure of synapses, with a selective enlargement of the active zones of asymmetric synapses and increased immunostaining for synaptic proteins marking inhibitory synapses.[173]

Given that EE is particularly effective in reducing GABAergic inhibition and in enhancing neurotrophin expression, it has great potential for therapeutic application in the treatment of DS. Martinez-Cué *et al.*[174,175] reported increased exploratory behaviour and enhanced spatial learning in EE Ts65Dn mice, although the effect was gender specific. At the cellular level, Ts65Dn mice raised in EE conditions have shown increased dendritic branching in the frontal cortex.[176] Despite these

results, a thorough analysis of the EE effects on mouse models of DS is still needed.

Alzheimer's disease. Alzheimer's disease is a neurodegenerative pathology leading to progressive memory loss and severe cognitive decline. The disease is characterized by two pathological hallmarks, mainly affecting the neocortex and hippocampus, that is, senile plaques (extracellular aggregates of β-amyloid derived from proteolysis of the precursor protein APP operated by the BACE enzyme) and neurofibrillary tangles (intraneuronal aggregations of hyperphosphorylated forms of the microtubule-associated protein tau).[177,178] In addition, as mentioned before, AD is invariantly associated with marked degeneration of BFCNs.[179] Most AD cases are sporadic and seem to result from an interaction of multiple genetic and still unknown environmental factors. However, there are also familial forms of AD that are inherited in an autosomal dominant manner. Three genes have been involved in familial AD: APP, presenilin 1 (PS1) and presenilin 2 (PS2). The main mutations at the levels of these genes have all been targeted in transgenic mouse modelling studies. A genetic risk factor for the sporadic form of AD has also been found in the ε4 polymorphism of the apolipoprotein E (APOE) gene.[180]

Levi *et al.*[181] were the first to examine the effect of differential rearing in a mouse model of AD, using transgenic mice expressing the human APOE3 or APOE4 alleles. Enriched mice transgenic for human APOE3 showed improved learning and memory associated with higher hippocampal levels of presynaptic protein synaptophysin and of NGF, whereas mice transgenic for human APOE4 were unaffected by EE. EE has repeatedly been reported to enhance performance in various cognitive tasks in transgenic mice carrying a double mutation at the level of both APP and PS1 genes,[182,183] in mice carrying the so-called Swedish mutation (SweAPP),[184–186] and in AD11 transgenic mice expressing a recombinant anti-NGF factor antibody.[187]

The effect of EE on Aβ levels and plaque deposition, as well as their impact on cognitive improvement, is controversial. Jankowsky *et al.*[182,188] unexpectedly reported that EE APP/PS1 transgenic mice develop a higher amyloid burden with increases in aggregated and total Aβ levels, particularly in the hippocampus. Arendash *et al.*[184] failed to observe any change in Aβ deposition in EE APP transgenic mice. In contrast, Lazarov *et al.*[189] reported a decrease in hippocampal and cortical Aβ levels and amyloid deposits in EE APP/PS1 transgenic animals compared with standard-housed controls. In addition, the enzymatic activity of neprilysin, an Aβ-degrading endopeptidase, was found to be elevated in the brain of EE mice.[189] A reduction in brain β-amyloid deposition after EE exposure has also been shown in APP, TgCRND8 and AD11 transgenic mice.[186,187,190,191] Some studies have also investigated the effects of EE on neurogenesis in AD mouse models. Although conditional PS1 knockout mice and mice overexpressing either wild-type human PS1 or the mutant form P117L show a deficiency in EE-induced neurogenesis,[192–194] it has been recently reported that EE promotes hippocampal neurogenesis in APP and TgCRND8 mice.[185,191,195] Moreover, EE increases angiogenesis and facilitates blood Aβ clearance through a differential regulation of Aβ receptor/transporter molecules in TgCRND8 mice.[196]

Lazarov *et al.*[189] carried out a microarray analysis to identify gene expression changes in APP/PS1 transgenic mice placed in EE conditions. This study revealed a total of 41 genes differentially regulated in response to EE, with the vast majority of genes that showed elevated expression encoding polypeptides involved in learning and memory, synaptic plasticity, neurogenesis, vasculogenesis, neuronal cell growth and cell survival pathways (e.g., NGF-1A, BDNF; CaMKIIα).[189] It is particularly interesting that transthyretin, a protein involved in Aβ clearance, is upregulated in transgenic mice raised with EE.[183] A quantitative RT-PCR study further confirmed that EE promotes the upregulation of trophic factor expression (NT-3, BDNF, IGF-I and VEGF) in the hippocampus of SweAPP mice.[185] Finally, environmental stimulation attenuates pro-oxidative processes and triggers anti-oxidative defence mechanisms, as indicated by diminished biomarkers for reactive oxygen and nitrogen species, downregulation of proinflammatory and pro-oxidative mediators and upregulation of superoxide dismutase 1 (SOD1) and SOD2.[197] Although the mechanisms underlying the beneficial effects of EE on mouse models of AD remain to be clarified in more detail, these studies indicate that an enhanced environmental stimulation may help in slowing down or preventing the cognitive decline associated with AD.

Conclusions

Altogether, the findings reviewed here show how dramatic the influence exerted by the environment can be on brain plasticity. Studies using the EE paradigm have indicated a number of molecular hotspots that might emerge as possible ways of accession for a successful treatment of neuropathological conditions affecting the juvenile and adult CNS. An open issue is the extent to which EE in animal models is relevant for the human living experience. EE is a complex paradigm, as an increased stimulation is provided at multiple sensory, motor, cognitive and social levels. Although most humans do experience a high degree of environmental complexity and novelty, levels of cognitive, social and physical stimulation vary greatly among individuals and in different periods of life. Strong correlative and epidemiological evidence shows that lifestyle, including occupation, leisure activities and physical exercise, has a direct effect on the risk of cognitive decline. Results indicate that a higher level and variety of mental and physical activity is associated with a lower cognitive decline and a reduced risk for dementia[198–204]. These results encourage stronger efforts in the application of EE paradigms, alone or in combination with pharmacological treatments, for the therapy of neurological disorders.

Conflict of interest

The authors declare no conflict of interest.

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