Does Experience Enhance Cognitive Flexibility? An Overview of the Evidence Provided by the Environmental Enrichment Studies

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Neuroplasticity accounts for the ability of the brain to change in both structure and function in consequence of life experiences. An enhanced stimulation provided by the environment is able to create a form of brain, neural, and cognitive reserve, which allows an individual to cope better with the environmental demands, also in case of neural damage leading to cognitive decline. With its complex manipulation of several stimuli, the animal experimental paradigm of environmental enrichment (EE) appears particularly effective in modulating the ability to successfully respond to the ever-changing characteristics of the environment. According to this point, it could be very relevant to analyze the specific effects of EE on cognitive flexibility (CF). CF could be defined as the ability to effectively change behavior in response to the environmental condition changing. This review article is specifically aimed to summarize and focus on the available evidence in relation to the effects of EE on CF. To this aim, findings obtained in behavioral tasks specifically structured to investigate animal CF, such as reversal learning and attentional set-shifting tests (tasks based on the request of responding to a rewarding rule that changes, within one or multiple perceptual dimensions), are reviewed. Data provided on the structural and biochemical correlates of these findings are also enumerated. Studies realized in healthy animals and also in pathological models are considered. On the whole, the summarized evidence clearly supports the specific beneficial effects of EE on CF. However, further studies on this key topic are strictly required to gain a comprehensive and detailed framework on the mechanisms by which an enhanced stimulation could improve CF.

Keywords: neuroplasticity, cerebral reserve, environmental enrichment, cognitive flexibility, animal models, rodents, reversal learning, attentional set-shifting

EXPERIENCE AND NEUROPLASTICITY

From the late 1940s, the idea that the brain has not a fixed structure but is characterized by a deep plasticity has been largely recognized (Hebb, 1949). As it is now known, every experience is translated in our brain in electrochemical messages, which allow us to feel, perceive, and elaborate information regarding each event occurring inside and outside the body. Such electrical activity induces plastic changes in the brain, both at a structural and at a functional level (Sale et al., 2014; Li et al., 2019). The ability of the brain to change in consequence of the experience is called *neuroplasticity* and is the basis of its successful coping with a number of situations, such as development, injury, and also usual learning and memory processes (Griesbach and Hovda, 2015; Gulyaeva, 2017).

Indeed, studies on cognitive decline demonstrated that such plastic changes could empower the brain with a form of "reserve." Namely, subjects with different sets of life experiences show different rate in developing physiological cognitive decline and/or dementia, with no linear correlation with brain structural degeneration (Stern, 2002; Perneczky et al., 2019). On this basis, the concept of cerebral reserve has been developed in relation to the experience-induced brain structure and function rearrangements that are able to support high-level performance in demanding situations and tasks, both in physiological and pathological conditions, which could be linked to age-related neurodegeneration or to other kinds of brain damage. The concept of reserve comprises a number of different levels, such as: (i) the *brain reserve*, that refers to the characteristics of the brain structural asset of an individual (such as brain volume; amount and morphology of neuronal and glial cells, blood vessels, and synapses; expression levels of neurotransmitters and neuromodulators; etc.); (ii) the *neural reserve*, that refers to the efficiency of the neural circuitry of an individual; and (iii) the *cognitive reserve*, that refers to the cognitive abilities and strategies recruited in cognitive and behavioral tasks by an individual (Serra et al., 2018; Stern et al., 2018; Serra and Gelfo, 2019). The reserve in its different aspects can be evaluated in subjects both in healthy and pathological conditions, by comparing them to subjects characterized by a lower level of experience-due stimulation in the previous life period.

It is widely agreed in the literature (Clare et al., 2017; Mandolesi et al., 2017; Chan et al., 2018; Pettigrew et al., 2019) that it is possible to identify three main lifestyle factors that induce a neuroprotective effect in the brain: (i) the *social factor*, that encompasses all the activities and engagements which include an individual in a high-level social network (such as familiar status; parentage; family ties; companionship; etc.; Bennett et al., 2014; Kuiper et al., 2016; Evans et al., 2018); (ii) the *cognitive factor*, that encompasses all the mentally demanding activities in which an individual could be significantly involved (such as education; occupational attainment; leisure activities; etc.; Yates et al., 2016; Grønkjær et al., 2019; Pudas and Rönnlund, in press); and (iii) the *physical factor*, that encompasses all the habits of healthy living maintained by an individual (such as motor activity; healthy dietary routines; intake of specific beneficial dietary components, such as ω-3 polyunsaturated fatty acid or antioxidants; abstention by alcohol massive assumption and smoking etc.; Lista and Sorrentino, 2010; Christie et al., 2017; Phillips, 2017; Blanchet et al., 2018; Rossi Dare et al., 2019). An enriching life-experience in the three listed dimensions seems to act just in an opposite and independent manner in respect to stressful early-life experiences, which appear to constitute a risk factor for vulnerability to pathological cognitive decline (Cabral et al., 2016; Caruso et al., 2018). On the other hand, it is important to add that usually, in human life-experience, these factors do not act independently, but are inter-related, and the brain structural, neural and functional status of an individual is the result of a sum of influences (Perneczky et al., 2019).

Clinical studies provided the cerebral reserve theory with large evidence. Nevertheless, some limitations of these studies have been highlighted, since genetic and life-experience peculiarities make humans hardly comparable on the basis of clearly defined and controlled variables (primarily due to the inter-related action of the listed factors in everyone life-experience). Moreover, a number of structural and biochemical aspects of the reserve are hardly evaluable in human *in vivo* studies (Petrosini et al., 2009; Gelfo et al., 2018; Serra et al., 2018; Serra and Gelfo, 2019). Such limitations could be overcome by modeling in animals the effects of the experience reported in humans, with the use of the environmental enrichment (EE) experimental paradigm.

THE ENVIRONMENTAL ENRICHMENT

The EE paradigm was introduced in the 1960s, to test in animals the effects of an enhanced social, cognitive and physical stimulation (Diamond et al., 1966; Rosenzweig and Bennett, 1996). The EE apparatus is frequently used with rodents, in comparison to the standard laboratory housing conditions (two/four animals/cage; standard cage size and bedding; *ad libitum* food and water; Nithianantharajah and Hannan, 2006, 2009). In this apparatus, by manipulating selected and well-defined variables for determined time-periods, it is possible to mimic the range of human experiences in relation to the three lifestyle factors: (i) the *social factor* is mimicked by housing the animals in groups larger than the usual ones; (ii) the *cognitive factor* is mimicked by housing the animals in complex environments, containing a lot of objects that are repeatedly substituted and repositioned, such introducing continuous elements of novelty; and (iii) the *physical factor* is mimicked by housing the animals in large cages that stimulate the exploratory movements, providing the cages with ladders and running wheels that allow motor activity, and also by offering to the animals specific supplementary diet elements (Baroncelli et al., 2010; Mo et al., 2016; Sampedro-Piquero and Begega, 2017). The EE paradigm represents a versatile mean to test the effects of all the involved factors or only one of them, by determining the starting, the end, and the duration of the exposure, and also by choosing the sensory channel to be mainly stimulated. Further, it is possible to determine also

if exposing to EE animals in healthy or pathological conditions (Simpson and Kelly, 2011; Toth et al., 2011; Dolivo and Taborsky, 2017; Gelfo et al., 2018).

On the whole, animal studies that investigated the effects of the exposure to EE stably reported an improvement in cognitive and behavioral performance, both in healthy and pathological conditions leading to cognitive decline (Leggio et al., 2005; Nithiananthanjah and Hannan, 2006, 2009; Petrosini et al., 2009; Foti et al., 2011; Hannan, 2014; Mandolesi et al., 2017). These results are accompanied by a strengthening of brain structure, neural circuitry and neurobiological processes (Kondo, 2017; Gelfo et al., 2018). More specifically, EE is reported to increase neurogenesis (Bergami, 2015; Sakalem et al., 2017; Kempermann, 2019), gliogenesis (Chakrabarti et al., 2011; Freund et al., 2013), angiogenesis (He et al., 2017), and synaptogenesis (Gelfo et al., 2009, 2016; Hirase and Shinohara, 2014). Also, a number of enhancing EE effects are described in relation to molecular processes, such as neurotrophic factor expression (Gelfo et al., 2011; Mosaferi et al., 2015; Novkovic et al., 2015) and neurotransmitter system functioning (Aumann, 2016; Gonçalves et al., 2018). With the support of an improved neural structure and functionality, the enriched animals show enhanced capacity to efficiently respond to the challenging situations proposed in the behavioral tasks, by utilizing high-level strategies in the performance. These enhanced capabilities have been largely investigated in learning and memory tasks (Pang and Hannan, 2013; Jin et al., 2017; Cortese et al., 2018; Bleimeister et al., 2019). However, since a relevant effect of EE is the augmented capability of adapting to and facing the ever-changing characteristics of the environment, an intriguing issue to be investigated could regard specifically the EE effects on cognitive flexibility (CF).

THE COGNITIVE FLEXIBILITY

The ability to maintain in memory the representations of the information previously encountered in everyone's experience is fundamental to successfully respond to the environmental stimuli; however, also the ability to efficiently update the retained information in consequence of the rapid changes of the environment is required for a successful adaptation (Bizon et al., 2012). CF could be defined just as the ability to shift associations and attentional sets in order to respond properly to the changing environmental conditions and demands; namely, CF is the ability to change behavior when environmental conditions change (Brigman et al., 2012; Nilsson et al., 2015). This fundamental process is encompassed among the *executive functions* (that also include working memory and inhibition), which make the individuals able to control adaptively their own thought and action (Buttelmann and Karbach, 2017). In humans, the gold standard to assess CF is the Wisconsin Card Sorting Test (Berg, 1948), which is structured to evaluate the ability to acquire association rules and attentional sets and to switch between them (Lange et al., 2017). In this test, after the acquisition of a card-sorting rule, the rule is changed, and the subject has to adapt the response to this shift. In rodents, CF is usually assessed by reversal learning or attentional

set-shifting tasks. Typically, in both kinds of task a rule of reward has to be learned by the animal, and then the rule is changed, and the animal has to respond to the new rule to gain the reward (Nilsson et al., 2015; Girotti et al., 2018). In the *reversal learning* tasks, the rule associates a single discriminatory stimulus—between two in the same perceptual dimension—with a reward; when the animal learns the rule, it is reversed (Talpos and Shoaib, 2015). Differently, the *attentional set-shifting* tasks usually involve more than one perceptual dimension, each containing more than one stimulus. In a first phase, the rewarded stimulus falls in a perceptual dimension; an *intradimensional shift* may be proposed, by changing the discrimination problem, but by rewarding always the same perceptual dimension. After the acquisition of the rewarding rule, a previously irrelevant perceptual dimension becomes relevant, and the rewarded stimulus is included in this other one (*extradimensional shift*, Chudasama, 2011; Tait et al., 2014; Heisler et al., 2015). On these two basic aspects, also more complex settings to assess CF have been developed, in which the rule to be acquired may imply the choice among or the learning of a sequence of potentially rewarded stimuli (Dalley et al., 2004; De Bartolo et al., 2009; Izquierdo et al., 2017).

Classically, CF has been associated with the functioning of prefrontal cortex (Kesner and Churchwell, 2011). Specifically, it has been showed in rodents that orbitofrontal cortex seems to support the performance in reversal learning tasks, whereas the regions of medial prefrontal cortex seem to be involved in attentional set-shifting tasks (Dalley et al., 2004; Brockett et al., 2015; Izquierdo et al., 2017). However, recent studies demonstrated that a larger circuitry is involved in the efficient attentional shifting; it has been advanced that it comprises also connections with the striatum and the amygdala (Klanker et al., 2013; Izquierdo et al., 2017). Also, several studies have evidenced that the cerebellum exerts a main role in modulating prefrontal cortex functioning in CF (De Bartolo et al., 2009; Dickson et al., 2010, 2017; Shipman and Green, in press). In addition, a key-function in CF has been devoted to new neurons that integrate themselves in hippocampal circuitry by neurogenesis (Anacker and Hen, 2017). A number of neurochemical factors have been indicated to modulate CF (Izquierdo et al., 2017; Girotti et al., 2018), which seems to involve different neurotransmitter systems, such as the cholinergic (Prado et al., 2017), dopaminergic (Izquierdo et al., 2006, 2010), noradrenergic (Logue and Gould, 2014), serotoninergic (Brigman et al., 2010), and glutamatergic (Jett et al., 2017) ones.

Impairments in CF are often characteristic of physiological and pathological aging, and such deficits are reported in several species (Bizon et al., 2012; Pfeffer et al., 2018). Moreover, deficits in CF characterize a number of neuropathological conditions, such as states of inflammation (Jurgens and Johnson, 2012), neurodevelopmental disorders (Whitehouse et al., 2017), schizophrenia (Saland and Rodefer, 2011), and Huntington's disease (Harrison et al., 2013; Curtin et al., 2016). According to this issue and to the fact that EE seems particularly suited to modulate the ability to successfully respond to the changing demands of the environment, it is noteworthy to specifically consider the EE effects on CF.

TABLE 1 | Studies referred to the environmental enrichment effects on cognitive flexibility in healthy animals.

Reference	Species (age or weight at the start of the environmental enrichment) / Environmental enrichment type and duration	Task assessing cognitive flexibility	Environmental enrichment effects
Brockett et al. (2015)	Male Sprague-Dawley rats (adult) / Free access to running wheel; 12 days	Attentional set-shifting task (including: reversal learning; intradimensional shift; extradimensional shift)	Enhanced performance in reversal learning and extradimensional shift. Enhanced synaptogenesis (hippocampus; medial prefrontal cortex; orbitofrontal cortex; perirhinal cortex) and gliogenesis (hippocampus; medial prefrontal cortex; orbitofrontal cortex)
Rountree-Harrison et al. (2018)	C57Bl6 mice (from birth) / Environmental enrichment—with running wheels; 74–93 days	Olfactory temporal order discrimination task (including: reversal learning; intradimensional shift)	Enhanced performance in reversal learning and intradimensional shift
Sampedro-Piquero et al. (2015)	Male Wistar rats (3.5 months) / Environmental enrichment: with vs. without forced exercise in Rotarod apparatus—no running wheels; 21 days	4-Radial arm water maze task (including: reversal learning; intradimensional shift)	Enhanced performance in reversal learning, without additive effect of forced exercise. Enhanced activation (c-Fos expression) in cingulate area of medial prefrontal cortex and orbitofrontal cortex
Schrijver et al. (2004)	Male Lister hooded rats (21 days) / Environmental enrichment: social vs. inanimate stimulations—no running wheels; 100 days	Two-choice discrimination task (including: reversal learning)	Enhanced performance in reversal learning (social stimulation). No effect in reversal learning (inanimate stimulation)
Zeleznikow-Johnston et al. (2017)	Male wild-type C57Bl/6J mice (4 weeks) / Environmental enrichment: no social manipulation—no running wheels; 10 weeks	Two-choice visual discrimination task (including: reversal learning)	Enhanced performance in reversal learning

Note: the characterization reported for the environmental enrichment paradigm specifies the variables manipulated, when variations on the classical complex paradigm (described in the article) are involved.

EFFECTS OF ENVIRONMENTAL ENRICHMENT ON COGNITIVE FLEXIBILITY

Given the large amount of experiments aimed to evaluate the EE effects on cognitive functions, a quite limited number of studies have been specifically devoted to investigate the EE effects on CF. By searching in PubMed for the references specifically related to EE and CF, without language and time-range limitations, and also by checking the references included in the relevant publications, the current state of the art appears to provide only 12 studies specifically devoted to the investigation of this topic.

As for the evidence in healthy animals, it has been demonstrated that a long-duration exposure to EE is able to improve the performance in tasks assessing CF, both in reversal learning and in intradimensional shift (Schrijver et al., 2004; Zeleznikow-Johnston et al., 2017; Rountree-Harrison et al., 2018). More specifically, Schrijver et al. (2004) reported that rats reared in EE (consisting in social enhanced stimulation) from weaning onwards showed in adulthood better performance in reversal learning compared to controls. This finding was not revealed after the exposure to EE consisting in inanimate stimulation. Differently, Zeleznikow-Johnston et al. (2017) reported that mice reared in EE (complex paradigm) from 4 weeks of age onwards showed in adulthood better performance in reversal learning in comparison to controls, also when social stimulation was not manipulated. Rountree-Harrison et al. (2018) confirmed that mice reared in EE (complex paradigm) from birth onwards showed in adulthood better performance in comparison to controls when tested in reversal learning, and also in intradimensional shift. Moreover, it has been demonstrated that also a brief-duration exposure to EE (complex paradigm) in adulthood is able to enhance CF performance (Brockett et al., 2015; Sampedro-Piquero et al., 2015). Sampedro-Piquero et al. (2015) showed that rats exposed to EE (complex paradigm) for 21 days in adulthood showed better performance in reversal learning; the combination of EE with a paradigm of forced exercise did not provide an additive effect. However, Brockett et al. (2015) found that rats exposed only to physical EE consisting in free running in wheels for 12 days in adulthood showed enhanced performance in reversal learning, and also in extradimensional shift. Functional effects of the exposure to EE were accompanied by enhanced activation, synaptogenesis and gliogenesis in hippocampus, perirhinal cortex, medial prefrontal cortex, and orbitofrontal cortex (Brockett et al., 2015; Sampedro-Piquero et al., 2015). Details on all of the studies cited in this section are provided in **Table 1**.

As for animal models mimicking aspects of human pathological conditions that provoke impairments in CF, evidence has been provided that EE exerts specific beneficial effects in tasks investigating this cognitive domain.

Specifically, it has been demonstrated that a long-term exposure (about 3 to 5 months) to EE (complex paradigm) is able to restore the performance in reversal learning both in transgenic (Pfeffer et al., 2018) and immunotoxic (De Bartolo et al., 2008) rodent models of Alzheimer's disease. In association, an augment in hippocampal neurogenesis and

TABLE 2 | Studies referred to the environmental enrichment effects on cognitive flexibility in pathological models.

Reference	Species (age or weight at the start of the environmental enrichment) *Environmental enrichment type and duration*	Pathological condition modeled	Task assessing cognitive flexibility	Environmental enrichment effect
Curtin et al. (2016)	Male and female zQ175 mice (7–8 weeks) *Early cognitive training; evaluation in adulthood*	Huntington's disease	Two-choice visual discrimination task (including: reversal learning)	Enhanced performance in reversal learning
De Bartolo et al. (2008)	Male Wistar rats (21 days) *Environmental enrichment—no running wheels; 5 months*	Alzheimer's disease (cholinergic immunotoxic depletion in the basal forebrain at 90 days)	Serial learning task (including: reversal learning)	Enhanced performance in reversal learning
Harrison et al. (2013)	Male R6/1 mice (5 weeks) *Access to running wheel (14 h/day; 5 days/week); 9/22 weeks*	Huntington's disease	Water T-maze set-shifting task (including: reversal learning)	Enhanced performance in reversal learning only after 22-week exposure. Reduction of striatal neuronal loss
Jurgens and Johnson (2012)	Male BALB/c mice (7 weeks) *Environmental enrichment—with running wheels; 4 months*	Influenza infection (inoculation with influenza A7PR8/34 virus at 6 months)	Morris water maze task - day 7 post-inoculation (including: reversal learning)	No effect in reversal learning. Reduction in hippocampal inflammation (proinflammatory cytokine expression)
Pfeffer et al. (2018)	Female APP23 mice (5 weeks) *Environmental enrichment—no running wheels; 1/12/24 weeks*	Alzheimer's disease	Morris water maze task (including: reversal learning)	Enhanced performance in reversal learning for young adults (12 weeks of exposure to EE). No effects after 1 or 24 weeks of exposure. Enhanced hippocampal neurogenesis in adolescent and young adult APP23 mice. Enhanced hippocampal gliogenesis in adult APP23 mice
Saland and Rodefer (2011)	Male Long Evans rats (51 days) *Environmental enrichment: free access to running wheels + enriched diet (alternation among water; saccharin solution; cookie); 1 h/day; 30 days*	Schizophrenia (phencyclidine HCl administration for 7 days starting at 66 days)	Two-choice discrimination task (including: reversal learning; intradimensional shift; extradimensional shift)	Enhanced performance in reversal learning and extradimensional shift
Whitehouse et al. (2017)	Female C58 mice (21 days) *Environmental enrichment: no social manipulation—with running wheels; 6 weeks*	Neurodevelopmental disorders (restricted and repetitive behavior)	Positional discrimination task (including: reversal learning)	Enhanced performance in reversal learning

Note: the characterization reported for the environmental enrichment paradigm specifies the variables manipulated, when variations on the classical complex paradigm (described in the article) are involved. Findings reported refer to enriched animals in comparison to non-enriched animals in the same pathological condition.

gliogenesis was reported (Pfeffer et al., 2018). A similar functional result has been shown in consequence of long-term cognitive or physical enrichment (about 15–22 weeks) in mouse models of Huntington's disease, with a reduction of the characteristic striatal neural loss (Harrison et al., 2013; Curtin et al., 2016). A 6-week exposure to EE without social manipulation (starting at weaning) has been demonstrated to enhance reversal learning also in a mouse model of neurodevelopmental disorder (Whitehouse et al., 2017). Moreover, in a rat model of schizophrenia, the exposure to physical enrichment only for 1 h a day for 30 days has been reported to improve performance both in reversal learning and extradimensional shift (Saland and Rodefer, 2011). Differently, in an adult mouse model of neuroinflammation (7-day inoculation of influenza virus), a previous 4-month exposure to EE (complex paradigm) failed in improve the performance in reversal learning, despite a reduction in hippocampal proinflammatory cytokines was reported (Jurgens and Johnson, 2012). Details on all of the studies cited in this section are provided in **Table 2**.

CONCLUSIONS

To the best of my knowledge, this is the first review of the scientific literature specifically aimed to summarize the evidence related to the effects of EE on the brain structure and function supporting CF. This one appears as a core issue since EE manipulation is particularly suited to modulate brain ability to cope with the changing demands of the environment. On the whole, this review article indicates that the exposure to EE is able to exert specific beneficial effects on CF performance when assessed both in reversal learning and in attentional set-shifting tasks. This evidence is confirmed both in healthy rodents and in pathological models.

However, a number of issues remain unclear, since the number of available studies is quite limited, and the applied experimental designs are very different in relation to several fundamental variables (such as age of EE starting; duration of the exposure to EE; gender of the animals; manipulated aspects; etc.; see above). Consequently, contrasting results are reported specifically in relation to the individual components of EE (social/cognitive/physical factors; see above). Also, not univocal results are provided in relation to the different aspects of CF assessed in the tasks (intradimensional/extradimensional shift; see above). In addition, structural and biochemical correlates of EE effects on CF functions appear still not deeply and completely investigated, since an integrated analysis on the complex circuitry and molecular pathways supporting CF has not still realized.

The reported contrasting findings obtained in animals are not considerably more clarifying than the data provided by research in humans, which reports conflicting evidence about beneficial effects of enhanced experience on executive functions, when evaluated in different domains and pathological conditions (Darby et al., 2017; Hindle et al., 2017; MacPherson et al., 2019). At the current status of investigation, animal studies seem not significantly take advantage of the superior chance of variable and measure control in respect to the human studies. Thus, while a stable indication on the specific beneficial effects of EE on CF can be gained from the current state of the art in animal scientific literature, a strong suggestion on the need of further studies specifically aimed to structure a clear framework on this topic is also revealed.

AUTHOR CONTRIBUTIONS

FG designed the project of this review, carried out the literature search and analysis, and wrote and edited the manuscript.

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