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Depression and adult neurogenesis: positive effects of the antidepressant fluoxetine and of physical exercise

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Highlights

- We review the correlation between depression/anxiety and adult neurogenesis
- Focus is on the antidepressant action of two neurogenic stimuli, fluoxetine and running
- Evidence pros and cons adult neurogenesis in humans and its role in depression
- The activation of neural stem cells by neurogenic stimuli is analyzed
- Fluoxetine or running effectiveness against depression in brain diseases and aging

ABSTRACT

Of wide interest for health is the relation existing between depression, a very common psychological illness, accompanied by anxiety and reduced ability to concentrate, and adult neurogenesis.

We will focus on two neurogenic stimuli, fluoxetine and physical exercise, both endowed with the ability to activate adult neurogenesis in the dentate gyrus of the hippocampus, known to be required for learning and memory, and both able to counteract depression. Fluoxetine belongs to the class of selective serotonin reuptake inhibitor (SSRI) antidepressants, which represent the most used pharmacological therapy; physical exercise has also been shown to effectively counteract depression symptoms in rodents as well as in humans.

While there is evidence that the antidepressant effect of fluoxetine requires its pro-neurogenic action, exerted by promoting proliferation, differentiation and survival of progenitor cells of the hippocampus, on the other hand fluoxetine exerts also neurogenesis-independent antidepressant effects by influencing the plasticity of the new neurons generated. Similarly, the antidepressant action of running also correlates with an increase of hippocampal neurogenesis and plasticity, although the gene pathways involved are only partially coincident with those of fluoxetine, such as those involved in serotonin metabolism and synapse formation.

We further discuss how extra-neurogenic actions are also suggested by the fact that, unlike running, fluoxetine is unable to stimulate neurogenesis during aging, but still displays antidepressant effects. Moreover, in specific conditions, fluoxetine or running activate not only progenitor but also stem cells, which normally are not stimulated; this fact reveals how stem cells have a long-term, hidden ability to self-renew and, more generally, that neurogenesis is subject to complex controls that may play a role in depression, such as the type of neurogenic stimulus or the state of the local niche.

Finally, we discuss how fluoxetine or running are effective in counteracting depression originated from stress or neurodegenerative diseases.

Keywords: Depression**,** Adult neurogenesis**,** Neurogenic stimuli**,** Running**,** Fluoxetine**,** Neural stem cells

1. Introduction

Depression is the most common psychiatric disorder, affecting more than 350 million people in the world (Smith, 2014). It is characterized by low mood, anxiety, anhedonia and reduced ability to concentrate (American Psychiatric Association, 1994; Perahia et al., 2009; Willner et al., 2013). The selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine are among the pharmaceutical drugs most used for therapy.
Several data indicate that the effect of antidepressants depends on their ability to induce hippocampal neurogenesis in rodents as well as in non-human primates (Santarelli et al., 2003; Kong et al., 2009; Mateus-Pinheiro et al., 2013; Perera et al., 2011). There are however conditions that induce resistance to antidepressants, which are related to several factors such as dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis or reduced ability to reactivate hippocampal neurogenesis (Belzung and Billette de Villemeur, 2010; El-Hage et al., 2013).

Neurogenesis continues during adulthood in two specific neurogenic niches, the dentate gyrus of the hippocampus and the subventricular zone (SVZ) adjacent to lateral ventricles, where new neurons are generated throughout life from stem cells (Kempermann et al., 2015; Lim and Alvarez-Buylla, 2016). The intrinsic structure of the hippocampus favors a sparsification of memory information from the entorhinal cortex, thus improving contextual and spatial learning processes in the mouse (Kesner et al., 2004) as well as in human (Bohbot and Corkin, 2007). Yet, hippocampal adult neurogenesis is required for learning and memory, in particular for pattern separation, i.e., the ability to disentangle similar memory patterns within the output to CA3; indeed this ability, although inherent to the dentate gyrus circuitry, is strongly enhanced from the addition of new neurons to the existing circuits (Aimone et al., 2011; Sahay et al., 2011; Tirone et al., 2013; Farioli-Vecchioli et al., 2008). On the other hand, the new neurons generated in the SVZ during adulthood migrate along the rostral migratory stream to the olfactory bulb, where they terminally differentiate into GABAergic inhibitory interneurons, that contribute to the olfactory function (Lim and Alvarez-Buylla, 2016). Interestingly, in pathological conditions such as brain trauma or stroke, the SVZ neurons are redirected toward the damaged area where they contribute to repair (Christie and Turnley, 2013).

Stem cells in the dentate gyrus have radial glia-like morphology and are localized in the subgranular zone; they express GFAP in their processes (Seri et al., 2001), as well as nestin and Sox2, and are named type-1 cells according to the nomenclature proposed by Kempermann et al. (2004; Steiner et al., 2006; Komitova and Eriksson, 2004). Stem cells mature into proliferating progenitor cells (type-2ab and type-3 cells); type-2a and type-2b are both nestin positive, the latter being positive also for the immature neuronal marker doublecortin (DCX), whose expression becomes prevalent in type-3 neuroblast cells (Filippov et al., 2003; Fukuda et al., 2003; Kronenberg et al., 2003). Progenitor cells evolve then into early postmitotic granule neurons, transiently expressing the Ca-binding protein calretinin (stage 5), and then become terminally differentiated neurons (stage 6) expressing calbindin (Brandt et al., 2003; Steiner et al., 2004).
Also in the other adult neurogenic niche, the SVZ, radial glia-like stem cells expressing GFAP generate proliferating transient amplifying cells (GFAP-negative Dlx-positive), which in turn generate DCX-positive migrating neuroblasts; these latter migrate to the olfactory bulb through the rostral migratory stream (Lim and Alvarez-Buylla, 2016).

After a first evidence indicating that adult neurogenesis occurs also in humans in the dentate gyrus (Eriksson et al., 1998), more recent data show that in the human dentate gyrus neurogenesis takes place at a rate of about 700 neurons generated per day and that the production of new neurons decreases steadily with age (Spalding et al., 2013; Knoth et al., 2010; Mathews et al., 2017). Interestingly, about 35% of the whole population of the dentate

gyrus in humans undergoes replacement (Spalding et al., 2013), while in the mouse this fraction is limited to only 10% (Imayoshi et al., 2008). However, opposite results were recently reported concerning the existence of adult neurogenesis in humans. In fact, Sorrells et al. (2018) did not detect neurogenesis in the human adult hippocampus from autoptic samples, whereas in adult macaques hippocampal neurogenesis was found. Conversely, Boldrini et al. (2018) observed a persistent neurogenesis during human life, from 14 to 79 years of age. This is also consistent with several previous reports in favour of human neurogenesis, observed also after neurogenic stimulation (Eriksson et al., 1998; Erickson et al., 2011). Very recently Kempermann proposed these conflicting data might be reconciled by hypothesizing that in adult humans the expansion phase is reduced, with a low number of precursor cells that remains proliferative, and is followed by a long postmitotic phase, during which DCX-negative neurons remain silent for a long period (Kempermann et al., 2018).

We will here discuss the effects of the antidepressant fluoxetine in relation to adult neurogenesis in comparison with another neurogenic stimulus, physical exercise, which, as we will see, has been shown to induce the remission of some depression symptoms in rodents as well as in humans and may thus play a role in support of the antidepressant therapy.

2. Correlation between anxiety/depression and neurogenesis in the rodent: dual action of fluoxetine and effects of running

As we will show, a positive modulation of neurogenesis by fluoxetine or by running correlates in rodents with amelioration of symptoms of anxiety/depression induced by stress (see for instance the paper by Mateus-Pinheiro et al., 2013) but also in models of neurodegenerative disorders such as Alzheimer's disease (Dong et al., 2004).

Mateus-Pinheiro et al. (2013) convincingly show that the absence of neurogenesis, caused by a neurotoxin, elicits depression-like symptoms in rats, revealed as lower performance in the sucrose consumption or forced swimming tests. These symptoms are reverted by fluoxetine provided that neurogenesis is not suppressed. Although there is a caveat for this report about the effectiveness of the neurotoxin used as suppressor of neurogenesis (Dupret et al., 2005), similar results are obtained in mice by David et al. (2009) after corticosterone-induced decrease of neurogenesis. Moreover, depression-like symptoms appear after 4 weeks, which is the period required for new neurons to be recruited into memory circuits.

Very interestingly, in a study by Hill et al. (2015) it has been shown that there is a direct correlation between anxiety/depression and neurogenesis, since by promoting neurogenesis in a mouse model through inactivation of the pro-apoptotic Bax gene in nestin-positive cells (i.e., neural progenitors), the symptoms of anxiety and depression-related behaviors induced by chronic treatment with corticosterone are reduced. These results match those obtained by the same group, showing that the antidepressant action of fluoxetine is not detected after ablation of neurogenesis by hippocampus irradiation (Santarelli et al., 2003). Another further proof that neurogenesis and fluoxetine-dependent antidepressive action are correlated comes from a study showing that in mice lacking the TrkB receptor in neural progenitor cells, where neurogenesis is impaired, no increase of dentate gyrus neurogenesis occurs after either running or fluoxetine treatment, and in parallel TrkB knockout mice become insensitive to antidepressive treatment in depression- and anxiety-like paradigms (Li et al., 2008).

There is however evidence that not all the antidepressant actions require neurogenesis and that the depletion of neurogenesis in itself is not directly causing anxiety/depression-like behavior (David et al., 2009; Henn and Vollmayr, 2004), a fact that may be partially reconciled by the existence of extra-neurogenic actions of antidepressants exerted on neural plasticity (see below section 6 "Effects of fluoxetine and physical exercise on the differentiation and plasticity of dentate gyrus cells"). Indeed, SSRIs antidepressants such as fluoxetine appear to have a dual action, being able to enhance the generation of new neurons as well as to facilitate their plastic functions, in line with the fact that serotonin (5-HT) is a key regulator of cell division, neuronal migration and differentiation, and also of processes

such as apoptosis, axon branching, and dendritogenesis (Gaspar et al., 2003); all this would favor the recovery of dysfunctional conditions such as depression, stress or anxiety (see for example Surget et al., 2011).

In analogy with that observed for fluoxetine, there is evidence that running ameliorates the symptoms of depression-like behavior - as judged by tests considered indicative of this state such as the forced swim and sucrose preference tests, a measure of anhedonia - in animal models of reduced neurogenesis, for instance in corticosterone-treated rats and in mice undergoing mild stress (Yau et al., 2011; Huang et al., 2017). The correlation between neurogenesis and depression is evident in a mouse model lacking adiponectin, where the neurogenic effect of exercise is abolished and at the same time the improvement of depression-like behavior is impaired (Yau et al., 2014). However, a similar requirement of adiponectin was observed for the environmental enrichment-induced relief of anxiety and depression-like symptoms, but in this case in a fashion independent from neurogenesis, indicating the existence of neurogenesis-independent pathways for depression (Nicolas et al., 2015).

Exercise has antidepressant-like and anxiolytic effects also in wild-type mice, as it improves the performance in classic tests measuring depression-like behavior (learned helplessness, forced-swim and tail suspension paradigms) and anxiety (elevated plus-maze and open field; Duman et al., 2008). A study performed in mice submitted in parallel either to treatment with fluoxetine or to voluntary running showed similar effects in terms of increase of neurogenesis, dendritic spine density within four weeks and amelioration of depression-like behavior (Huang et al., 2012). Moreover, the gene patterns modified by fluoxetine and exercise were mostly common, such as the activation of genes involved in membrane and synapsis (such as NPTX2 or BDNF) and/or proteasome function, suggesting antidepressant mechanisms partially shared that may impact on synapsis remodeling (Huang et al., 2012). Further evidence shows that depression-like behavior induced by stress (restraint, cold or forced swimming) and the concomitant reduction of neurogenesis and blood vessel density are rescued by exercise, whose action resulted to require an active vascular endothelial growth factor (VEGF) pathway (Kiuchi et al., 2012). The improvement of blood vessel, in correlation with that of neurogenesis, is thus brought in play in antidepression mechanisms. Another study implies in the antidepressant action of running not only BDNF, important for the maturation of neurons, but also MIF (macrophage migration inhibitory factor); in fact running increased neurogenesis and in parallel MIF, which in turn augmented BDNF as well as serotonin levels, while depletion or overexpression of MIF increased or reduced, respectively, depression-like symptoms in rodents (Moon et al., 2012).

Therefore, exercise induces antidepressant actions and mechanisms that appear to be related to an increase of neurogenesis; however, exercise triggers several plastic processes in the dentate gyrus that may not be directly related to neurogenesis (described in section 6 “Effects of fluoxetine and physical exercise on the differentiation and plasticity of adult dentate gyrus cells”), thus it seems reasonable to expect these as well to play a role in the antidepressant effects by exercise, comparably to that seen for fluoxetine.

3. Correlation between depression and neurogenesis in humans

The key question arising is whether depression and neurogenesis are correlated also in humans. Several studies performed using magnetic resonance imaging (MRI) in patients with depression showed a decreased hippocampal volume relative to controls, without difference in the whole brain (Sheline et al., 1996; Bremner et al., 2000; Campbell et al., 2004; Videbech and Ravnkilde, 2004). Similarly, in post mortem studies of depressed patients a tighter packing density of glia and granule cell neurons in the hippocampus emerged (Stockmeier et al., 2004). All this led to the idea that decline of adult neurogenesis and depression are correlated in human (Jacobs, 2002). A first caveat, that we reviewed in the Introduction, concerns the possibility that adult neurogenesis occurs indeed in humans, a subject on which reports in favor or against continue to appear. It is worth noting that, while such a correlation

between neurogenesis and depression is still debated today, Czéh and Lucassen (2007) suggested that rather than a decrease of absolute neuron number, hippocampal function may be affected by a decreased turnover within hippocampal circuits. On the other hand, MRI of patients diagnosed with depression and under treatment for 3 years with antidepressants (including fluoxetine) showed an increased volume of the left hippocampus, which also correlated with a better clinical outcome versus patients with smaller hippocampal volume (Frodl et al., 2008). Moreover, depressed patients appear to show an increase of anxiety, which has been attributed to a confused integration of incoming stimuli and ultimately to a defect of pattern separation; fluoxetine appears to relieve anxiety in humans as well as in animals (Kheirbek and Hen, 2014).

Concerning physical exercise, there is a large number of studies that support the efficacy of exercise in reducing symptoms of depression in patients (see for review Craft and Perna, 2004; Schuch et al., 2016). A study even shows that 16 weeks of aerobic exercise was equally effective as antidepressants in reducing depression among aged patients with major depressive disorder (Blumenthal et al., 1999). There is also indirect evidence that physical exercise elicits neurogenesis in humans, since Erickson et al. (2011) found in a single-blind, randomized trial in older adults that aerobic exercise leads to increased volume of about 2% in the anterior hippocampus, which within the medial temporal lobe contains the dentate gyrus. This increase - which corresponds to the approximate loss occurring every one or two years of aging - induced improvements in spatial memory. Moreover, physical activity improves cognition also in elderly Alzheimer's disease (AD) patients (Kemoun et al., 2010). Thus, exercise can induce significant structural changes in the brain and protect against age-related neuronal loss and functional decline. Overall, as long as we consider valid the evidence of adult neurogenesis in humans, even if in a reduced form, this suggests that the correlation between exercise and neurogenesis could be realized also in humans, although it is likely that this correlation is only a part of the depression paradigm.

4. Effects of fluoxetine and exercise on the proliferation of adult dentate gyrus and SVZ cells

In general the monoaminergic antidepressants have been shown to activate cell proliferation and survival of newborn neurons in rats and mice (Malberg et al., 2000; Encinas et al., 2006).

Notably, the effect on proliferation and survival of monoaminergic antidepressants including fluoxetine are slow to take place, since chronic but not subchronic treatment is effective (Malberg et al., 2000; Duman et al., 2001; Santarelli et al., 2003; David et al., 2010; Wang et al., 2008). However, it has been observed that fluoxetine begins to induce a slight increase of proliferating $BrdU^+$ cells in the hippocampus after 5 days (Malberg et al., 2000), which becomes significant after 7 days (Micheli et al., 2017).

It has been shown that fluoxetine induces the proliferation of dividing dentate gyrus type-2 and type-3 progenitor cells, but, notably, is ineffective on stem cells (type-1; Encinas et al., 2006).

There are, however, examples of lack of effect on the proliferation of progenitor cells in the dentate gyrus by fluoxetine, for instance see Hanson et al. (2011), or Navailles et al. (2008) and Klomp et al., (2014), where an effect of fluoxetine on adult hippocampal neurogenesis was observed only when treatment started during adolescence. Moreover, fluoxetine is unable to induce neurogenesis in the SVZ (Ohira and Miyakawa, 2011; Nasrallah et al., 2010; Kodama et al., 2004), but appears to be active in the prelimbic cortex (Kodama et al., 2004). Nevertheless, fluoxetine is able to restore the decrease of neurons observed in the rostral migratory stream and olfactory bulb after corticosterone treatment, as well as the depression-like state associated, suggesting that also the SVZ and olfactory bulb may be implicated in depression; in fact numerous clinical investigations uncover olfactory impairment in patients suffering from major depression (Siopi et al., 2016). Likewise, chronic fluoxetine rescues the

deficit of neurogenesis observed directly in the SVZ of mice stressed by forced swimming (Hitoshi et al., 2007).
Voluntary physical exercise is also a very effective inducer of adult neurogenesis in the dentate gyrus (van Praag et al., 1999a,b; Vivar et al., 2013). The increase of proliferation of progenitor cells ($Ki67^+$) occurs rapidly, as early as after 3 days of voluntary running (Patten et al., 2013).
However, running is not effective as an inducer of neurogenesis in the SVZ (Brown et al., 2003), as observed for fluoxetine. Yet, an increase of SVZ neurogenesis by running is observed in some conditions, namely, in old mice (Blackmore et al., 2009), or when voluntary running is prolonged (Bednarczyk et al., 2009) or in mice with deletion of Btg1, a gene maintaining quiescence of neural stem cells (Mastrorilli et al., 2017), or also after stress induced by corticosterone infusion (Lee et al., 2016).

5. Cognitive effects of fluoxetine and exercise in rodents and humans

Despite the large circumstantial evidence that spatial learning requires hippocampal neurogenesis (Deng et al., 2010; Farioli-Vecchioli et al., 2008; Dupret et al., 2008), the increase by fluoxetine of dentate gyrus neurogenesis does not correspond to a univocal increase of cognitive behavior. In fact, on the one hand there is evidence in favor of cognitive improvement in mice after fluoxetine treatment, namely, of enhanced learning (Meneses and Hong, 1995) or of increase of a form of neurogenesis-dependent long-term potentiation (LTP) in the dentate gyrus (Wang et al., 2008), as well as of memory improvement in humans (Levkovitz et al., 2002). Additionally, chronic fluoxetine reduces pharmacologically-induced depression like-behavior (in the tail suspension and forced swim tests; Popa et al., 2008), and has a favorable effect on hippocampus-dependent memory in the water maze and passive avoidance tests after prenatal exposure to high doses of fluoxetine (Bairy et al., 2007). Remarkably, Popa et al. (2008) demonstrated, using mice where the 5-HT reuptake has been removed either transiently or permanently, that anxiety and depression-related behaviors are dissociable.
On the other hand, there is evidence that fluoxetine treatment in rodents has no effect on spatial memory (Morris water maze test; Keith et al., 2007; Valluzzi and Chan, 2007; Grunbaum-Novak et al., 2008; Stewart and Reid, 2000) or even has a negative effect in open field and avoidance response (Nelson et al., 1997; Ulak et al., 2006) or increases depression-like symptoms after prenatal exposure (forced swimming test, Lisboa et al., 2007) and, in humans, causes impairments of episodic memory (Wadsworth et al., 2005).
One possible explanation for these discrepancies has been put forward by a study of Satvat et al. (2012), which showed that, in rats treated with fluoxetine for 24 days and following a washout period of five weeks, the new neurons generated (identified as $BrdU^+NeuN^+$cells) accumulated in the lower blade of the dentate gyrus and were positive for Arc, indicating that the new neurons were functional and had been recruited into active memory circuits. However, no change in spatial memory was observed, and the point raised by the authors is that the ventral region of the dentate gyrus is more implicated in anxiety than in memory (Bannerman et al., 2004), for which, instead, the dorsal region is more responsible (Kjelstrup et al., 2002). In fact contextual memory (fear conditioning) as well as spatial navigational memory are not affected by lesions in the ventral dentate gyrus (Kjelstrup et al., 2002). Moreover, it has been found by Anacker et al. (2018) that adult-born neurons have an inhibitory action on a specific subset of stress-responsive neural cells in the ventral dentate gyrus.
As for running, there is straightforward evidence that, in parallel with the surge of proliferation of progenitor cells, it induces an increase of performance in different hippocampus-dependent cognitive tasks, such as spatial memory and spatial pattern separation (Voss et al., 2013; Creer et al., 2010), or novel object recognition (Bolz et al., 2015) and contextual fear conditioning (Kohman et al., 2012). Physical exercise leads to

improvements in spatial memory also in humans (Erickson et al., 2011). Notably, running, unlike fluoxetine increases neurogenesis in the dorsal, but not in the ventral region of the dentate gyrus (Vivar et al., 2016), a finding that satisfactorily correlates the different types of cognitive response induced by the two stimuli with the different area of the dentate gyrus activated by them.

Whether these differences in cognitive response and in localization of neurogenic activation in the dentate gyrus elicited by fluoxetine and running are indeed related to differences in rescue of depression symptoms is an open question. If we accept the result of meta-analyses in humans indicating that also physical exercise has significant antidepressant effect in patients with depression (Schuch et al., 2016), it seems plausible that fluoxetine and exercise, by impacting on different areas of the dentate gyrus, at least as defined by experiments in rodents, can be effective on different sets of depression symptoms. In this respect, fluoxetine may be more effective on symptoms related to anxiety/depression rather than to memory, at least in tests on mice, such as defined by the open field test, which measures anxiety and where running is inactive (Marlatt et al., 2010). Moreover, the ventral DG is the area most implicated in the etiology of depression (Bannerman et al., 2004), and in humans, the ventral hippocampus is connected to amygdala, prefrontal cortex and nucleus accumbens, areas implicated in emotional and reward pathways.

6. Effects of fluoxetine and physical exercise on the differentiation and plasticity of adult dentate gyrus cells

Fluoxetine, in addition to the proliferative action, is also able to accelerate the maturation of immature DCX^+ cells, as reported by Wang et al. (2008). Consistently, we also observed a mild but significant increase by chronic fluoxetine treatment in the rate of terminal differentiation of stage 6 adult neurons (identified as $BrdU^+calretinin^-NeuN^+$ cells; Micheli et al., 2017). This pro-differentiation effect is also in line with the finding that fluoxetine induces the expression of BDNF in dentate gyrus cells, where it exerts a marked influence on their maturation (Molteni et al., 2006; Waterhouse et al., 2012). Similarly, also running or the norepinephrine reuptake inhibitor reboxetine increase the levels of BDNF, in a CREB-dependent fashion (Chen and Russo-Neustadt, 2009).

However, Encinas et al. (2006) did not detect such a pro-differentiation effect by fluoxetine and, according to Kobayashi et al. (2010), fluoxetine chronic treatment reduces the number of $calbindin^+$ terminally differentiated neurons, an effect observed also by McAvoy et al. (2015). Kobayashi et al. (2010) propose this effect to be a "dematuration" of mature granule neurons, possibly through 5-HT4 receptors. This decrease of $calbindin^+$ neurons, however, is an expected finding when using a protocol where no time interval after treatment is given to the newly generated progenitor cells in order to allow them to differentiate, since in that case the proliferative action of fluoxetine will prevail (see for instance Micheli et al., 2017). It is worth noting that the dematuration effect described by Kobayashi et al. could be the expression or the result of the ability of fluoxetine to induce synaptic/neural plasticity, described by Wang et al. (2008) or Beauquis et al. (2009), which may certainly contribute to the antidepressive action by facilitating the recruitment of new neurons into existing circuits. The pro-differentiation effect of fluoxetine may be limited also by its ability to reduce BMP4 expression, which may result in a decreased entry into quiescence and differentiation (Brooker et al., 2017, see below).

Also exercise stimulates neural differentiation, as indicated for instance by the increase of DCX^+ cells in the dentate gyrus of cyclooxygenase-2 (COX-2) knockout mice after treadmill, where these are in lower number (Nam et al., 2013). However, the stimulation of the maturation of new neurons by exercise appears to have a longer latency (about two weeks) than the increase of proliferation, which is almost immediate (Patten et al., 2013).

Remarkably, running, similarly to fluoxetine, enhances also the plasticity of new neurons, by increasing dendritic complexity and spine density (Eadie et al., 2005; Stranahan et al., 2007) as well as the short-term synaptic plasticity from lateral entorhinal cortex, thus favoring the integration of contextual and spatial information (Vivar et al., 2016, 2013). It seems, however, that long-term exercise is required to stably enhance synaptic plasticity in the hippocampus, since a recent study showed that dentate gyrus cells showed a reliable increase of LTP only after 56 days of running (Patten et al., 2013). To the plastic changes in cytoarchitecture elicited by running correspond changes in synaptic proteins (Hu et al., 2009), glutamate receptors (Farmer et al., 2004), plasticity-related genes, growth factors and neurotransmitters in the dentate gyrus (Molteni et al., 2002; Lista and Sorrentino, 2010).
Overall, although some of these changes, such as dendritic complexity, are a direct consequence of increased neurogenesis (i.e., proliferation), it seems reasonable that an increase of neural plasticity elicited by running may play a neurogenesis-independent role in the rescue of depression symptoms, with a dual action as observed for fluoxetine. We should also consider that obviously not only the absolute number of new neurons but also their correct functionality is critical for hippocampal activity (Tirone et al., 2013).

7. Mechanisms of action of fluoxetine and of running on proliferation and differentiation of adult progenitor cells and neurons

The proliferative effect of fluoxetine on progenitor cells may be the consequence of several actions, including an increased survival, but mainly it could depend on the increase of serotonin on 5-HT1,3,4,6,7 receptors localized in the hippocampus that regulate proliferation (Alenina and Klempin, 2015). As observed by Santarelli et al. (2003), the ablation of 5-HT1a receptors disables the neurogenic action of fluoxetine, thus pointing to a key role of this specific receptor. More recently, it has been found that 5-HT1a receptors are involved in the acute stimulation of the self renewal of precursor cells, whereas 5-HT2c receptors - which in the long term stimulate an increase of late-stage progenitor cells and early postmitotic neurons - may antagonize the acute effect of 5-HT1a receptors, thus causing the known delay in fluoxetine effect (Klempin et al., 2010). Of note, the same increase of proliferation of dentate gyrus progenitor cells is obtained when 5-HTergic neurons are depleted in adult mice with conditional knockouts activated by diphtheria toxin or tamoxifen, depending on the extent of the depletion (Song et al., 2017); this may confirm that 5-HT receptors, which have about 15 subtypes (Homberg et al., 2010), have multiple and contrasting actions, and that the effect of fluoxetine is the net result of different effects.
Moreover, fluoxetine has been shown to inhibit the expression of the cell cycle inhibitor p21Cip1 (Pechnick et al., 2011). Interestingly, despite the strong pro-proliferative action, fluoxetine is devoid of effects on the length of the cycle of wild-type stem and progenitor cells (Micheli et al., 2017), unlike what we have observed for another neurogenic stimulus, i.e., physical exercise, which reduces the cycle length of progenitor cells (Farioli-Vecchioli et al., 2014b). It is worth noting, however, that in a specific condition such as the knockout of the antiproliferative gene Tis21, also fluoxetine has been seen to accelerate the kinetic of the S-phase of cell cycle of dentate gyrus progenitor cells (Micheli et al., 2017).
Very interestingly, fluoxetine and other antidepressants negatively modulate hippocampal bone morphogenetic protein (BMP). In fact fluoxetine suppresses BMP signaling in the adult mouse hippocampus by both decreasing the levels of BMP4 and increasing the levels of the BMP inhibitor noggin. Likewise, overexpression of BMP4 blocked the effects of fluoxetine on proliferation of dentate gyrus cells, while noggin infused into lateral ventricles exerted antidepressant activity (Brooker et al., 2017). Thus, BMP signaling in the hippocampus may control depressive behavior, and a decrease of BMP signaling may be required for the effects of some antidepressants. It has been shown that BMP4 brings stem/progenitor cells of the dentate gyrus to quiescence, thus displaying an antiproliferative action (Mira et al., 2010). However, BMP4 also shows a positive action on neuroblast maturation, an effect particularly evident in the SVZ, where BMP4 is able to rescue a defect of differentiation consequent to

the ablation of the pro-differentiative gene Tis21, inducer of BMP4 (Farioli-Vecchioli et al., 2014a).
Thus, the decrease of BMP4 effected by fluoxetine may impair the ability of fluoxetine to induce the differentiation of dentate gyrus cells, exerted through BDNF. Moreover, the transcription factor CREB - which activates BDNF expression - has also been involved in depression, being activated by antidepressants; however, contradictory effects were observed, since CREB-deficient mice show a rapid behavioral response to antidepressants, accompanied by upregulation of neurogenesis (Gass and Riva, 2007).
Concerning physical exercise, several hypotheses have been forwarded to explain its pro-neurogenic effect on progenitor cells in the dentate gyrus (Overall et al., 2016). These propose that running: i) induces the generation of progenitor cells and neurons by increasing their survival; ii) increases the number of cell divisions possibly after extra-neurogenic divisions; iii) recruits quiescent stem cells; see a detailed discussion below in section 9 "Effects of fluoxetine and running on stem cells of the dentate gyrus". One additional possibility proposed by us is that the level of enhancement of neurogenesis induced by running may also depend on the kinetic of the S-phase of the cell cycle (Farioli-Vecchioli et al., 2014b), whose acceleration might be seen as a stabilizing action for the increase of proliferation, rather than a causal action, since the increase of proliferation induced by running probably preceeds the cell cycle acceleration (see Farioli-Vecchioli and Tirone, 2015; Mastrorilli et al., 2017). In fact, a report in which an acute protocol of running was used (five days), showed that no change occurs in the cell cycle length of dentate gyrus progenitor cells (Fischer et al., 2014). Yet, SVZ stem/neuroblast cells of Btg1 knockout mice presented a decrease of the cell cycle length detectable after a short period of running (five days), suggesting that the change in cell cycle length, being quite early, could be, at least in the SVZ and in specific conditions, a relevant factor involved in the process of stem/progenitor cells expansion (Mastrorilli et al., 2017).
Intriguingly, it has been shown that the pro-proliferative effect of voluntary wheel running requires the release of central serotonin in young adult and aged mice, whereas the absence of brain serotonin causes alterations at the stage of Sox2-positive precursor cells (Klempin et al., 2013). All this suggests that serotonin is a common mechanism shared by antidepressants and exercise and that both may impact on depression. It is also worth noting that BDNF appears to be an important positive modulator of synaptic plasticity and memory through neurotrophins pathways not only for fluoxetine but also for running (Sleiman and Chao, 2015).
Similarly to that observed for fluoxetine, BMP4 as well has been found to play a role in the proneurogenic effects of running, since the levels of BMP4 are reduced by running (Gobeske et al., 2009).
A key mediator of the increase of neurogenesis by running is also adiponectin, a protein secreted from adipocytes, which acts through its own receptor (Yau et al., 2014). However, as mentioned above, adiponectin is necessary for the rescue of depression-like symptoms not only in a neurogenesis-dependent fashion (Yau et al., 2014) but also neurogenesis-independent (Nicolas et al., 2015).
Insulin-like growth factor I (IGF-I) levels in serum also play a role in exercise-dependent neurogenesis and anxiety as well as in spatial learning, but not in depression-like behavior (i.e., behavioral despair measured by forced swimming; Trejo et al., 2008).

8. Pro-survival/antiapoptotic effects of fluoxetine and exercise

It has been shown that depression in humans is associated to the activation of inflammatory pathways, with an increase of pro-inflammatory cytokines such as interleukin-1beta (IL1beta), interleukin-6 (IL6) and tumor necrosis factor-alfa (TNF-alfa; Schiepers et al., 2005; Raison et al., 2006). Interestingly, a depressive state activates immune cells (Hoseinzadeh et al., 2016). Fluoxetine, in turn, has been demonstrated to have a neuroprotective effect through an antinflammatory action against microglia activation, as it

reduces the production of IL1beta and IL6 as well as of TNF-alfa (Liu et al., 2011; Zhang et al., 2012).
However, fluoxetine is also endowed with a specific antiapoptotic effect, which appears to be associated with increase of the antiapoptotic gene Bcl-2 in the rat hippocampus and also in the frontal cortex and striatum (Réus et al., 2012). Moreover, some studies indicate that the increase of Bcl-2 expression exerted by fluoxetine and other antidepressants may depend on the increase of BDNF levels, which is known to be involved in survival pathways and controls the expression of apoptotic and antiapoptotic proteins (Manji et al., 2001). Consistently, stress is known to reduce the expression of Bcl2 (Kosten et al., 2008). As a result of this antiapoptotic action, the in vivo survival of new neurons in the hippocampus is greatly increased by fluoxetine treatment (Encinas et al., 2006; Micheli et al., 2017).
Similarly, running increases cell survival as well as BDNF levels and the phosphorylation of AKT, a key gene for cell survival signaling (Chen and Russo-Neustadt, 2009). Furthermore, treadmill exercise in a rat model of Alzheimer's disease decreased the expression of the pro-apoptotic gene Bax and increased the levels of Bcl-2 (Baek and Kim, 2016). Voluntary exercise has clearly neuroprotective actions, as the use of running wheel before a controlled cortical trauma prevents extensive neuronal loss in the dentate gyrus as well as CA1, CA2/3 hippocampal regions, prevents microglia activation and increase of the pro-apotoptic genes Bid and PUMA (Zhao et al., 2015).

9. Effects of fluoxetine and running on stem cells of the dentate gyrus and SVZ

The functional definition of stem cells in the dentate gyrus adopted here is referred to either quiescent or proliferating radial glia $GFAP^+nestin^+Sox2^+$ cells (named type-1, according to Kempermann et al., 2004), while in the SVZ this refers to $GFAP^+$ or $nestin^+Sox2^+$ cells residing in proximity of the ventricles (Lim and Alvarez-Buylla, 2016). These cells are at the origin of the ongoing neurogenesis and their activation by neurogenic stimuli is regulated by a network of quiescence-maintaining genes.
There is no evidence that fluoxetine is able to activate the proliferation of type-1 stem cells in the dentate gyrus, rather that it strongly activates the proliferation of type-2ab and type-3 cells (Encinas et al., 2006; Micheli et al., 2017).
Moreover, although fluoxetine is unable to induce neurogenesis in the SVZ, as mentioned above (in the section 4 "Effects of fluoxetine and exercise on the proliferation of adult dentate gyrus and SVZ cells"), fluoxetine, and imipramine as well, is able to rescue to control levels the number of SVZ stem cells (primary neurospheres) reduced by a condition of chronic stress occurring after forced swim (Hitoshi et al., 2007).
Concerning physical exercise, several reports show that proliferating type-1 stem cells are not increased by running (Kronenberg et al., 2003; Steiner et al., 2008; Brandt et al., 2010). Moreover, Suh et al. (2007) showed increase after running of $BrdU^+Sox2^+$ cells, which include not only stem cells but also proliferating type-2ab transit amplifying cells, which are $Sox2^+$ (Komitova and Eriksson, 2004; Steiner et al., 2006). Nevertheless, Lugert et al. (2010) showed that there is a subpopulation of quiescent radial neural stem cells, expressing Hes5 and labeled in a specific mouse model by GFP, which are responding to running. Thus, this mouse model may have identified a subpopulation of responsive neural stem cells or, alternatively, this may be a model-specific feature.
However, we have shown that stem (type-1) cells of the dentate gyrus can be induced to proliferate by both fluoxetine and running, after their proliferative capability has been reduced following deletion of the antiproliferative gene Btg1, which is responsible for the maintenance of the quiescence of stem cells in the dentate gyrus and SVZ (Farioli-Vecchioli et al., 2014b, 2012; Micheli et al., 2018). The number of Btg1-null mitotic stem cells increased by running or fluoxetine is considerably above the number of control stem cells (about three-fold and 40% higher, respectively), a fact that clearly indicates how stem cells are endowed with a reserve potential which under specific conditions is revealed. In fact, the

activation of neurogenesis after the end of the running exercise persists in Btg1-null dentate gyrus longer than in controls (3 months versus one month; Farioli-Vecchioli et al., 2014b) and might be correlated to the acceleration of the S-phase of stem and progenitor cells, which may stabilize their process of amplification. Such a reactivation by running is observed also in Btg1-null stem cells of the SVZ with depleted proliferative capability (Mastrorilli et al., 2017). Notably, neurogenesis in the SVZ is not normally increased by exercise (Brown et al., 2003; see section 4 "Effects of fluoxetine and exercise on the proliferation of adult dentate gyrus and SVZ cells"), although it has been observed that in aged mice running is able to stimulate the division of SVZ stem cells (Blackmore et al., 2009).
Conversely, after deletion of the quiescence-maintaining gene Notch1, which reduces the number of stem cells in the dentate gyrus, running is unable to rescue this decrease, despite the large increase of neurogenesis (Ables et al., 2010). Moreover, there is also evidence that after deletion of the antiproliferative cyclin-dependent kinase inhibitor (CDKI) p57, running is unable to enhance the number of stem cells in the dentate gyrus (Furutachi et al., 2013).
Further studies are necessary to define the effects of neurogenic stimuli on the regulation exerted by CDKI genes maintaining the quiescence of stem and progenitor cells either in SVZ, such as the CDKIs p21Cip1 (Kippin et al., 2005), or p27Kip1 in the dentate gyrus (Hörster et al., 2017). See Table 1 and Table 2 for summary of this section on stem cells.

Looking at other neurogenic stimuli, it turns out that neural stem cells seem to be increased in the number entering the cell cycle after brain injury (Gao et al., 2009). Similarly, systemic treatment with the glutamate agonist kainic acid (Huttmann et al., 2003), or electroconvulsive shock (Segi-Nishida et al., 2008) induces their number.
As a whole, this suggests that the activation of stem cells, i.e., their entry in mitosis, is protected by a network of antiproliferative genes whose function is to maintain quiescence. Such an ability appears to be not generalized to all the genes that inhibit proliferation of stem cells or that are deputed to maintain their quiescence. Hence, defining the extent of this gene network may help understand the functional meaning of quiescence and the regulation of the proliferation of neural stem cells.
Two theories have been proposed about the regulation of stem cell self-renewal and maintenance, one by Bonaguidi et al. (2011) supporting the idea of a sustained ability for self-renewal, the other by Encinas et al. (2011) favoring a deterministic view of a steady "disposal" of stem cells, being converted into neurons and astrocytes. The above data indicate that in certain conditions, such as deletion of specific genes maintaining quiescence and/or in the presence of a strong neurogenic stimulus, there is room for an expanded self-renewal of hippocampal and SVZ stem cells, without, however, excluding that the hidden flexibility of this control may be curtailed after an extended period of enhanced self-renewal.

10. Effects of fluoxetine on neurogenesis are age-dependent while effects of running are age-independent

It is known that at older age neurogenesis decreases, in terms of both progenitor cells and neurons that are generated (Kuhn et al., 1996; Rao et al., 2006).
On the other hand, the action of fluoxetine, as well as of other SSRIs, on depression- and anxiety-like behaviors is age-dependent (see for review Olivier et al., 2011). It seems possible that at the origin of the inactivity of fluoxetine in older age is the decrease of serotonin transporter (SERT) expression observed during aging in the hippocampus as well as in raphe nuclei and cortex (Herrera-Perez et al., 2013). In fact, fluoxetine induced an increase of survival and neurogenesis in 3 month-old mice but not in older mice (6 to 12 month-old; Couillard-Despres et al., 2009; Li et al., 2015; McAvoy et al., 2015). Also the age-dependent spatial memory impairment (as judged by novel object placement) was not rescued by fluoxetine in middle-aged mice (12 month-old), although vortioxetine, a multimodal antidepressant, succeeded (Li et al., 2015). Nevertheless, the hippocampus of middle-aged mice resulted more sensitive than younger mice to synaptic remodelling induced by

fluoxetine, in terms of increased dendritic spine density (McAvoy et al., 2015). Consistently, fluoxetine led to an increase of contextual memory and antidepressant-like behavior, although accompanied by a greater arousal expressed in higher levels of anxiety (McAvoy et al., 2015). Moreover, we have recently observed that in mice with deletion of the quiescence-maintaining gene Btg1, fluoxetine induces neurogenesis by increasing the number of stem and type-2 progenitor cells in the dentate gyrus also of aged mice (15-month-old), indicating that in specific conditions stem/progenitor cells can be activated by fluoxetine during aging (Micheli et al., 2018).

At any rate, it is worth noting that the lack of induction of neurogenesis by fluoxetine in normal, older mice may imply that in aged humans its antidepressant effect, which is clearly detectable (Zoric et al., 2018), might be independent of neurogenesis.

In contrast, physical exercise is able to overcome the age-dependent decline of hippocampal neurogenesis; running is indeed effective in 9 to 20 month-old rodents in restoring neurogenesis of at least 50% of the control level of young animals, and also the morphology of young neurons and BDNF levels, as well as spatial memory (Morris water maze and place recognition tests; van Praag et al., 2005; Siette et al., 2013; Marlatt et al., 2012).

11. Effects of fluoxetine or exercise in brain diseases

11.1. Stress

Stress is one leading cause for depression. In fact both can be associated with a reduced ability to generate new hippocampal neurons as well as with high plasma glucocorticoids (Jacobs, 2002; Kempermann, 2002; Warner-Schmidt and Duman, 2006). These features are present not only in different types of depression, but also in aging and diabetes (Beauquis et al., 2009). It has been shown that antidepressants, including fluoxetine, can restore the defect of neurogenesis in all these conditions (Duman et al., 2001; Malberg, 2004; Beauquis et al., 2009). Moreover, the recent finding of stress-responsive cells in the ventral dentate gyrus, inhibited by adult-born neurons, links stress to neurogenesis (Anacker et al., 2018).

Indeed, it has been found that chronic stress decreases neurogenesis not only in the dentate gyrus but also in the SVZ, especially when using a forced-swim model, where neural stem cells are reduced by stress; fluoxetine is able to revert this deficit (Czéh et al., 2007; Hitoshi et al., 2007). Similarly, as mentioned above, chronic corticosterone treatment evokes an anxiety/depression-like state with a decrease of bulbar and hippocampal neurogenesis accompanied by reduced olfactory acuity and memory; all these symptoms are restored by fluoxetine treatment (Siopi et al., 2016). Moreover, it has been shown that fluoxetine (and to a lesser extent desipramine) counteracts the deficit of neurogenesis induced in the dentate gyrus - but not in the SVZ - by learned helplessness, a model of depression elicited by repeated stress (Chen et al., 2006).

It is also worth mentioning the attempts with specific stress protocols associated to ablation of neurogenesis, designed to distinguish among neurogenesis-dependent and -independent actions of fluoxetine and their benefit for depression and anxiety. The importance of this approach is that it aims at defining whether neurogenesis is indeed involved in the onset of depression. In summary, the results of several experiments indicated very clearly that in rodents undergoing chronic mild stress or stress induced by corticosterone and whose neurogenesis has been ablated, some behavioral depression-like signs are ameliorated independently of neurogenesis, while some others are dependent (Airan et al., 2007; Bessa et al., 2009; Surget et al., 2008; David et al., 2009). For instance, in the corticosterone-stress model the effects of antidepressants on novelty suppressed feeding are neurogenesis-dependent while the open field effects are independent (David et al., 2009); or, in the chronic mild stress model, the fluoxetine effects on novelty suppressed feeding are dependent on neurogenesis while the forced swim test is not dependent (Bessa et al., 2009). A thorough analysis by Mateus-Pinehiro et al. (2013), with protocols of stress associated to neurogenesis depletion, shows that neurogenesis induced by an antidepressant such as fluoxetine is

essential for the long-term recovery from emotional and cognitive impairments associated to a depression-like state, although some behavioral alterations do not correlate with variations in neurogenesis.

Although the ablation of hippocampal neurogenesis is never completely effective (Tirone et al., 2013), these data as a whole indicate that the majority of antidepressant and antianxiety actions require an active neurogenesis, but also suggest that amelioration of stress-induced depression may depend as well on the ability of antidepressants to promote neural plasticity.

Moreover, there is clear evidence today that the hypothalamus-pituitary axis (HPA) is hyperactive in major depressive disorders and that this antagonizes the action of antidepressants (Belzung and Billette de Villemeur, 2010). A model has been devised to create resistance to antidepressants, where chronic mild stress, which activates/deregulates the HPA axis (Surget et al., 2011), is followed by corticosterone suppression with dexamethasone; in this model it has been found that fluoxetine is able to restore the impaired hippocampal neurogenesis only in those mice with higher suppression (HS) of corticosterone levels (Khemissi et al., 2014). Although the mechanisms need to be clarified, this example draws a correlation among intensity of stress, corticosterone levels, and resistance to antidepressants through deregulation of the HPA axis. Another earlier report also shows that suppression by dexamethasone of induced stress is less effective in suppressing depression-like behaviors in mice deficient for neurogenesis, thus implying a role for hippocampus as critical negative control of the HPA axis (Snyder et al., 2011).

Also mice with diabetes, induced by streptozotocin, show reduced neurogenesis, which is restored to normal levels by chronic fluoxetine (Beauquis et al., 2009). Indeed, diabetes leads to an augmented susceptibility to stress correlated to high glucocorticoid plasmatic levels and to hyperactivity of the HPA axis (Magariños and McEwen, 2000).

Concerning the effects of running, several reports indicate that physical exercise also rescues the decrease of neurogenesis induced by stress in adult as well as in old mice (Kannangara et al., 2011). In fact, running counteracted the cognitive deficit and restored the decrease of neural proliferation following chronic corticosterone treatment in both the dentate gyrus (Yau et al., 2012) and the SVZ (Lee et al., 2016). Similarly, with another type of induction of stress (chronic restraint stress), running rescued the deficit of dentate gyrus cell proliferation and of cognitive function (tested by Morris water maze; Nakajima et al., 2010). In terms of mechanisms involved, it appears that stress (developmentally induced by maternal separation) increases telomere length in ventral hippocampus, an effect counteracted by running (Botha et al., 2012).

11.2. Neurodegenerative diseases

11.2.1. Alzheimer's disease

Alzheimer's disease (AD), the most common form of dementia, is characterized by a progressively severe loss of hippocampus-dependent memory and deterioration of cognitive functions (Jacobs et al., 1995; Goedert and Spillantini, 2006). The hippocampus is particularly stricken and heavily affected in AD. This decrease of memory has been associated not only to loss of neurons but also to impairment of the maturation and differentiation of neural progenitor cells (Lazarov and Demars, 2012; Mu and Gage, 2011). Hallmarks of AD are the accumulation within neurons of neurofibrillary tangles, resulting from the hyperphosphorylation of the cytoskeletal tau protein, and the formation of senile plaques generated from the extracellular accumulation of the amyloid beta peptide (Aβ); this is the product of an altered metabolism of the human amyloid precursor protein (APP), which is cleaved and accumulates as neurotoxic amyloid plaques within the extracellular space of AD brains (see Hamdane and Buée, 2007; Lazarov and Demars, 2012, for review).

Fluoxetine, which turns out to be a widely used antidepressant to treat the depression and anxiety associated with AD, also improves spatial memory, learning and emotional behaviors of APP/PS1 mice, possibly by inhibiting APP T668 phosphorylation, thus causing a reduced accumulation of Aβ (Wang et al., 2014). The APP/PS1 mouse model carries the mutations

APPswe/PS1ΔE9, which induce as a very early symptom a decrease of neurogenesis in the dentate gyrus, indicating that APP or PS1 and their metabolites negatively modulate adult hippocampal neurogenesis (Demars et al., 2010). Similarly, the Tg2576 transgenic mice, overexpressing the "Swedish" mutation in the human amyloid precursor protein 695, show reduced proliferation in the dentate gyrus associated with impairments in contextual memory, but all these symptoms are counteracted by fluoxetine administration (Dong et al., 2004).
Concerning voluntary exercise, for example it has been shown that prolonged running in the 3xTg AD mouse model did increase neurogenesis (in terms of progenitor cells survival) without effects on differentiation and no evident influence on the AD pathology (Marlatt et al., 2013). On the other hand, in the APP/PS1 transgenic mice, ten weeks of treadmill training increased the hippocampus-dependent memory and decreased the levels of soluble Aβ in the hippocampus (Lin et al., 2015).

11.2.2. Parkinson's disease

Parkinson's disease (PD), whose neuropathological hallmark is the aggregation of α-synuclein in substantia nigra, locus ceruleus, and nucleus basalis, is characterized by neuropsychiatric symptoms such as depression and anxiety that precede the onset of motor symptoms (Polymeropoulos et al., 1997). A loss of serotonergic neurons or their projections into the hippocampus and modifications in the release of serotonin may be connected to these symptoms. 4-5 month-old A53T αSyn transgenic mice, overexpressing human mutated α-synuclein, present hippocampal dysfunction and impairment of neurogenesis, which is reversed by chronic fluoxetine treatment that increases hippocampal dentate gyrus neural precursor cell proliferation and differentiation into neurons, ascribed to increased BDNF and GDNF levels (Kohl et al., 2012).
Furthermore, in PD patients fluoxetine is being used as adjuvant therapy to reduce neurodegeneration and inflammation, or more generally, the depression symptoms, and is effective in rodent models of PD as well as of multiple system atrophy, a disease conducive to PD (Zhang et al., 2015; Boggio et al., 2005; Palma and Kaufmann, 2015). For example, in the rat treated in the substantia nigra with lipopolysaccharide (LPS), which causes loss of dopaminergic neurons, fluoxetine injections prevented further degeneration; this may have been related to a reduced microglial activation (Chung et al., 2010). Finally, it appears that fluoxetine has a beneficial effect on PD also by upregulating the risk-attenuating genes of PD Skp1a and Aldh1a1 (Lauterbach, 2013).
Concerning running, there is evidence that in the MPTP-lesioned mouse model exercise does increase cognitive performances, reducing anxiety and increasing learning on the elevated plus maze test, but without effects on tests of depression-like state (Gorton et al., 2010).

11.2.3. Huntington's disease

Huntington's disease (HD) is a complex genetic neurodegenerative disease caused by an expanded CAG trinucleotide repeat encoding a polyglutamine tract in the huntingtin protein, characterized by abnormal motor symptoms, accompanied by depression and degeneration of the striatum and also of the hippocampus (Walker, 2007). In patients, a study shows that fluoxetine may prevent progression of the disease (De Marchi et al., 2001), while another did not find conclusive evidence (Moulton et al., 2014). Interestingly, however, transgenic HD mice R6/1 have decreased hippocampal cell proliferation with hippocampal-dependent cognitive and depressive-like behavioral symptoms, which are relieved by fluoxetine treatment (Grote et al., 2005).
Similarly, voluntary running in the same transgenic HD mouse model R6/1 delays some motor symptoms (rear-paw clasping) and ameliorates cognitive deficits without, however, rescuing motor coordination defects (Pang et al., 2006).

12. Effects on depression of combined exercise and fluoxetine treatment

The reports reviewed here provide examples indicating that running and fluoxetine may have a similar but not fully overlapping spectrum of action on anxiety and depression-like behavior

tests. Thus, an issue worth to be discussed for its implication in the treatment of depression, is the combined effect of fluoxetine treatment and exercise and whether they synergize.
For instance, Lapmanee et al. (2013) observed in stressed rats (by restraint) that running was effective in reducing anxiety-like behaviors in both elevated plus-maze and elevated t-maze tests, but fluoxetine was effective only in the latter, while both running and fluoxetine reduced depression-like behavior in forced swimming tests. No synergy was observed. In another condition of stress (induced postpartum by corticosterone) Gobinath et al. (2018) found that only running was able to reduce depression-like symptoms (forced swim test); however, only fluoxetine prevented anhedonia (loss of maternal care), but without synergy with running in either test. Moreover, in a situation of strong stress (inescapable stress) Greenwood et al. (2007) found that only running counteracted anxiety-like behavior (freezing behavior and escape latency) as well as a decrease of BDNF levels in the dentate gyrus; combined fluoxetine and running did not change the result. No synergy either was observed for the ability to increase BDNF levels in normal conditions (Engesser-Cesar et al., 2007).
However, Shafia et al., 2017 found that, after a prolonged stress, the extinction of inhibitory avoidance, a test measuring anxiety, was increased by physical exercise (moderate treadmill) or by fluoxetine, and the effect was more pronounced when they were combined.
All this suggests that the antidepressant action of fluoxetine and running, although not additive in the majority of cases, may usefully complement each other to reduce the different types of depression/anxiety-like symptoms.

13. Conclusions

A key question is whether adult neurogenesis plays a causal role in depression. Certainly, there is evidence that the antidepressant action of fluoxetine requires an active neurogenesis. However, fluoxetine has a dual action, being also able to enhance the plasticity of new neurons, which has been associated with an antidepressant activity independent from neurogenesis. Moreover, although the ablation of neurogenesis does not result in anxiety/depression-like symptoms (according to David et al., 2009), neurogenesis in human displays a higher turnover than in rodents (Spalding et al., 2013; Imayoshi et al., 2008), suggesting that small changes in turnover of new neurons may be relevant to the onset of depression (Czéh and Lucassen, 2007).
It is also worth noting that in aged mice fluoxetine has still antidepressant action but is unable to trigger neurogenesis, suggesting that during aging the antidepressant effect is independent from the production of new neurons. Conversely, running, which displays antidepressant effects, has a pro-neurogenic action which is age-independent. Moreover, in specific conditions, such as after stress or ablation of genes that inhibit proliferation, fluoxetine (in the dentate gyrus, Micheli et al., 2018, and in the SVZ, Hitoshi et al., 2007) or running (in the dentate gyrus as well as in the SVZ; Farioli-Vecchioli et al., 2014b; Blackmore et al., 2009) activate not only progenitor but also stem cells. This, on one hand suggests that the control of neurogenesis and self-renewal is adaptable to the ongoing cell state, in accordance with the proposal by Bonaguidi et al. (2011), and on the other hand that the correlation between neurogenesis and depression may depend on many variables, such as the type and duration of the neurogenic stimulus, the genetic background, or the state of the local niche.
Another significant effect concerns the ability of fluoxetine or running to counteract depression also when consequent to stress (with both neurogenesis-dependent and -independent actions) or to neurodegenerative diseases, although in this latter case they are not always able to reduce neurodegenerative symptoms.

Conflict of interest

The authors report no conflict of interest.

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Tables

Table 1. Activation of stem cells in the adult dentate gyrus by fluoxetine or running.

Neurogenic stimulus	Activation of dentate gyrus stem cells (Type-1; $BrdU^+GFAP^+nestin^+Sox2^+$)	Activation of progenitor cells (type-2-3)	Cognitive effects	References
Fluoxetine	NO	YES	--	Encinas et al., 2006; Micheli et al., 2017
Fluoxetine	YES	YES	--	Micheli et al., 2018
Running	NO	YES	--	Kronenberg et al., 2003; Steiner et al., 2008; Brandt et al., 2010
Running	NO ($BrdU^+$ $Sox2^+$→ type-2a)	YES	--	Suh et al., 2007
Running	YES ($Hes5\text{-}GFP^+$ cells)	--	--	Lugert et al., 2010
Running	YES (only after deletion of the quiescence gene Btg1)	YES	Rescue of defective contextual discrimination	Farioli-Vecchioli et al., 2014b
Running	NO (after deletion of the quiescence gene Notch)	YES	--	Ables et al., 2010
Running	NO (after deletion of the antiproliferative gene p57)	--	--	Furutachi et al., 2013

Table 2. Activation of stem cells in the adult SVZ by fluoxetine or running.

Neurogenic stimulus	Activation of SVZ stem cells (Ki67/BrdU$^+$ GFAP or nestin/sox2$^+$)	Activation of SVZ neuroblasts/neurons (Ki67/Brdu$^+$ and/or DCX$^+$ or NeuN$^+$)	Cognitive effects	References
Fluoxetine	NO	NO	--	Ohira and Miyakawa, 2011; Nasrallah et al., 2010; Kodama et al., 2004
Fluoxetine	--	YES (after corticosterone-induced depression-like state)	Rescue of depression-like state and of olfactory acuity	Siopi et al., 2016
Running	YES (in old mice; neurospheres)	YES (in old mice; BrdU$^+$ cells)	--	Blackmore et al., 2009
Running	--	YES (prolonged running; DCX$^+$ or BrdU/Ki67$^+$)	--	Bednarczyk et al., 2009
Running	YES (after deletion of the quiescence gene Btg1; in adult as well as old mice)	YES (after deletion of the quiescence gene Btg1)	Rescue of neurons recruited to olfactory circuits	Mastrorilli et al., 2017