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A systematic review of the effect of stress in animals during adolescence, and its long-term consequences during adulthood: focus on hippocampal neurogenesis, cognitive function and behavioural outcomes

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Abstract

Adolescence represents a critical period for the programming of future adult behaviours. Neurogenesis is particularly active during adolescence, with increased number of granule cells and increased hippocampal volume both in animals and humans. Among the factors which can affect neurogenesis during adolescence, stress is considered a major one. Indeed, adolescence is known to be a particularly stressful period in life, with some adolescents suffering from mood disorders and anxiety. While there is increasing interest on the neurogenic changes occurring during the adolescent period, evidence is sparse. We conducted a systematic review summarising changes in hippocampal neurogenesis, neuroplasticity and hippocampal-dependent cognitive functions and behavioural outcomes in stress-induced adolescent animal models of depression, and investigating long-term stress effects on the same outcomes assessing the same animals in adulthood. Overall, the results show a significant reduction in hippocampal cell proliferation, and a concomitant increase in depressive-like behaviours in adolescent animals exposed to stress challenges, however reduction in the number of surviving neurons was accompanied by no changes in both cognition and behaviour. Studies also observed altered neuroplasticity, including a stress-induced decrease in markers of pre- and post-synaptic plasticity, dendritic spine length and density, and long-term potentiation. These changes in neuroplasticity were accompanied by cognitive impairments and depressive-like behaviours. Overall, some of the negative effects observed during adolescence, especially on cell proliferation, neuroplasticity, cognition and behaviour either persisted or worsened during adulthood. Interestingly, treatment during adolescence with antidepressants, glutamate receptor inhibitors, glucocorticoid antagonists, or a healthy diet consisting of omega-3 fatty acids and vitamin A, were able to reverse or prevent these detrimental effects. Future research should aim to investigate the translational impact of these preclinical findings, developing novel tools for the measurement of hippocampal neurogenesis directly in depressed adolescents, and subsequently assessing

neurogenic changes in response to stress as well as pharmacological and non-pharmacological interventions.

INTRODUCTION

Adolescence represents a fundamental time for transition into adulthood, and a critical period for the programming of future adult behaviours [1, 2]. In animals (mice and rats) adolescence spans from post-natal day (PND) 21 to 65, and in humans from 12 to 18 years of age [3], and represents a time of intense behavioural and neurodevelopmental changes [3, 4] (Figure 1). Modifications of the reward circuitry, both in rodent and humans, has been shown to affect adolescents' sensitivity to aversive effects of drugs of abuse [5]. From a behavioural perspective, adolescent rodents [4–6] and humans [4] show increased social activity [7], risk-taking [8] and impulsivity [6]. Moreover, cognitive changes that occur in adolescence [9], especially with respect to executive functions [10] and cognitive control [11], are suggested to be related to brain neurodevelopmental changes including maturation of circuits that are critical for learning and memory, particularly the hippocampus [12].

The adolescent hippocampus has been shown to have more granule cells and larger volume in both rodents and humans, compared to adulthood [13, 14]. Of note, hippocampal neurogenesis, defined as the generation of new neurons within the subgranular zone and their integration in the granule cell layer of the dentate gyrus (DG) [15], is four times higher in adolescence compared with adulthood in both rodents and humans [16]. While the exact advantage of having a higher number of new born hippocampal neurons is still to be fully understood [17], evidence generated from animal and human post-mortem studies suggests that neurogenesis is necessary for antidepressant efficacy [18–21], and that reduction in neurogenesis, upon stress exposure, can negatively affect cognitive performance [22], and induce depressive-like behaviours [23].

Factors that detrimentally affect neurogenesis during adolescence include stress exposure [24]. The period of transition from adolescence to adulthood is known to be associated with psychosocial or physical stressors [3], and in England more than one in seven young people (15.3%) aged 11–19 develop at least one psychiatric disorder [25, 26]. In animals, chronic exposure to stressful situations, including psychosocial stress, decreases adult hippocampal neurogenesis in mice, rats, and primates, and results in impaired hippocampal-dependent learning and memory, and depressive-like behaviours, which can last until adulthood [27, 28]. The mechanisms through which stress exposure reduces neurogenesis remain largely unknown, but may involve increased cortisol and inflammatory cytokines [29]. We have shown that exposing human hippocampal progenitor cells to cortisol or cytokines *in vitro*, results in a reduced pool of neural progenitor cells, decreased neurogenesis and an increased number of mature apoptotic neurons [30–38].

While it has been hypothesised that pruning and neurogenic changes have a role in in shaping brain circuits, and consequently emotional, cognitive, and behavioural functions during adolescence, few studies have addressed this question. A relatively limited number of preclinical studies have examined hippocampal neurogenesis, cognitive and behavioural changes during adolescence upon exposure to stressful challenges. Even a lower number of studies has conducted further investigations to understand whether these effects persist later in life. Indeed, adolescence is a critical period for the onset of brain disorders, such as schizophrenia and depression, that are characterised by cognitive and emotional symptoms which persist into adulthood [39]. Changes in neurogenesis during adolescence may affect the preservation and integration of emotional memories, and the selection of memories that are maintained versus those that are filed away [40–42], contributing to the genesis of cognitive and behavioural symptoms. As such, understanding how hippocampal neurogenesis is affected during adolescence is important, not only from a mechanistic perspective, but also for the development of novel therapeutic strategies (or for the repurposing of existing ones) targeting neurogenic mechanisms.

This is the first *systematic* review of the available literature investigating changes in hippocampal neurogenesis, and hippocampal-dependent cognitive functions and behavioural outcomes, in adolescent animal stress models of depression, and examining long-term outcomes lasting into adulthood. In addition, this review discusses findings from studies employing either pharmacological or non-pharmacological interventions as possible therapeutic strategies to reverse or prevent neurogenesis modifications, cognition and behaviour.

METHODS

We searched PubMed, Embase, Psycinfo and Web of Science for studies assessing hippocampal neurogenesis in adolescent animals exposed to stress models of depression. The included models used biological stressors, such as cortisol or cytokine injections, or behavioural stress paradigms, applied during adolescence (from PND21 to PND65 [28]) in either rats or mice, and measured neurogenesis as well as hippocampal-dependent cognitive functions, such as memory and learning, and depressive-like behaviour, in the same period. We included measures of neurogenesis, using markers labelling cells at specific developmental stages, from cell proliferation to neuronal differentiation (doublecortin (DCX), NeuN) [43] in animals previously exposed to a stress challenge. We examined studies that assessed cell proliferation using Bromodeoxyuridine (BrdU), a marker injected either weeks and/or briefly before sacrifice, to measure respectively new-born neuron differentiation and survival, and progenitor cell proliferation [44]. We also included studies that assessed cell proliferation using Ki67, a marker expressed by any cell during mitosis except in phase G0. We further included studies analysing measures of neuroplasticity after adolescence stress exposure, using markers of cell integration and synaptic plasticity (pre- and post-synaptic density proteins, long-term potentiation), as well as neurotrophic factors. Indeed, investigating neuroplasticity allows to understand how newly generated neurons are ultimately integrating and remodelling the existing circuits.

The complete inclusion and exclusion criteria, and the search algorithm, can be found in the Supplementary Materials. In total, 905 studies were extracted and 37 of these were selected after screening (Supplementary Figure 1). Subsequently, studies were assessed for risk of bias, including failing to describe animals baseline characteristics, random housing or blinding, following the SYRCLE guidelines for animal studies [45] (Supplementary Table 1). The results of these studies are summarised in Table 1.

RESULTS

Amongst the thirty-seven studies meeting our inclusion criteria, all of them reported measures of markers of hippocampal neurogenesis and neuroplasticity after stress exposure during adolescence, and six of them had additional measures in adulthood to investigate the longer-term effects of adolescent stress. The specific timing and type of adolescent stress, as well as of neurogenesis and neuroplasticity measures, and cognitive and behavioural assessment, are reported in Table 1.

Adolescence

Changes in hippocampal neurogenesis, and hippocampal-dependent cognitive and behavioural outcomes

Seven studies assessed changes in proliferation using non-co-labelled BrdU, which therefore detects any type of cell that is proliferating. Among these studies, five reported a decrease in cell proliferation in stress exposed compared with non-exposed animals, independently of the type and length of stressor used, social defeat (PND24-34 and PND30), social instability (PND30-45, PND28-46), or cortisol administration (PND28-48) [46–50]. In contrast, two studies observed no changes in cell proliferation upon the exposure of animals to crowding or social isolation at PND28 and PND2-49, respectively [51, 52]. When assessing emotional and cognitive functional changes associated with fewer BrdU proliferating cells, one study showed no link between lower proliferation and memory deficits [46]. However, increased depressive-like behaviour was observed with decreased BrdU in two studies [48,

50], but not in a third [49]. Thus, evidence points towards a link between decreased DG cell proliferation and depressive-like behaviour.

Results from measuring proliferation using non-co-labelled Ki67, a marker detecting cells at any phase of mitosis except G0 (a broader mitosis marker than BrdU), showed an initial increase in Ki67 labeling at PND33 that was no longer present at PND46 in one study [53], decreased Ki67 at PND35 in another, and no changes at PND49 in a third study [46, 49], possibly indicating that while there could be a proliferation decrease early on close to stress exposure, hippocampal cell proliferation might go back to normal later on. Furthermore, this effect was independent of the type of stress, social defeat or social instability, and length of stress exposure, PND24-34 [49], PND30-45 [46, 53]. In addition, these results of decreased proliferation with stress at PND24-34 and PND30-45 were accompanied by no significant changes in cognitive function and depressive-like behaviour [46, 49, 53].

In addition to measuring cell proliferation using non-co-labelled BrdU and Ki67, five studies measured the negative effects of adolescent stress exposure on neuronal differentiation and maturation using DCX. Despite the controversy regarding the specificity of DCX as a neurogenesis marker, DCX has been largely used to assess numbers of neuroblasts or immature neurons in rodents, human, and non-human primates [43]. Two studies assessing the effects of acute stress, reported a decrease in DCX positive cells in rodent DG at PND42 and PND63, respectively [47, 54]. This effect was independent of the type of stress, being social defeat or interleukin (IL)-1beta treatment. However, two studies assessing the effects of chronic stress, reported no changes at PND42 and PND56 after exposure to restraint stress at PND42-56 and chronic mild stress (CMS) at PND28-42 [55, 56], and an increase at PND65, when compared with unexposed animals [55]. Similarly, another study reported an increase in DCX positive cells at PND46 after exposure to social instability stress at PND30-45 [53, 55]. These affects were accompanied by no significant changes in cognitive function and depressive-like behaviour [53, 54, 56]. We have reported that in resilient individuals, with early

life adversity exposure that did not develop lifetime psychopathology , the DG had more granule neuron tissue[57]. These findings are in line with the reports in mice, showing that animals unaffected by the stress might have more neurogenesis as a coping mechanism to stress exposure.

Finally, three studies quantified cells labelled by BrdU in co-localization with the neuronal marker NeuN, and performing BrdU injections three weeks before sacrifice. Although one study did not show any difference in new-born neuron number in animals exposed to chronic cortisol treatment (PND28-48 [50]), two studies reported a reduction in the number of surviving new-born neurons upon chronic exposure to social defeat or social isolation at PND24-34 and PND21-49, respectively [49, 51]. Interestingly, these effects were reversed by mifepristone, a glucocorticoid receptor (GR) antagonist [49], and fluoxetine [51]. However, across these studies, cognitive function and depressive-like behaviour were not affected [49, 50].

Changes in neuroplasticity markers, hippocampal-dependent cognitive functions and behavioural outcomes

Eight studies measured changes in markers of synapse formation and neuroplastic activity after adolescent stress was induced. Importantly, post-synaptic density 95 (PSD95), used to label the formation of postsynaptic processes during and after maturation of neurons, was decreased in three studies [58–60] together with the pre-synaptic marker synaptophysin (SYN) [60], upon exposure to chronic stress with either cortisol, CMS or social defeat stress at PND29-49, PND28-61 and PND35-44, respectively [58–60]. These decreases in PSD95 were accompanied by increased depressive-like behaviour [59, 60]. In contrast, both PSD95 and SYN were unaffected in two studies upon exposure to chronic stress with cortisol or social isolation at PND29-59 and PNDP30-35, respectively [61, 62], and no changes in memory or depressive-like behaviours were observed [62]. Overall, these studies show a decrease in synaptic density in adolescent stress, accompanied by increased depressive-like behaviour.

Additionally, proteins expressed in presence of neuroplastic activity, such as polysialylated-neural cell adhesion molecule (PSA-NCAM) and neural cell adhesion molecule L1 (NCAM-L1), were increased in two studies upon exposure to juvenile stress at PND27-29 and PND28-42, respectively [63, 64]. In contrast, no changes in PSA-NCAM expression, as well as memory, were observed in a third study upon exposure to chronic peripubertal stress at PND28-42 [65]. Similarly, other neuroplastic proteins, such as the immediate early gene Arc, involved in the consolidation of memories, was increased in two studies upon exposure to restraint stress and social defeat stress at PND21 and PND45-46, respectively [66, 67], whereas Erg1, involved in learning and memory, was decreased in one of the two aforementioned studies [67]. However, while PSA-NCAM has previously been observed to be increased in the hippocampus in models of depression, it is also associated with decreased neurogenesis, highlighting the need to further study these markers alongside more direct markers of neurogenesis [68, 69].

Six studies also showed dysfunctions in synaptic transmission, namely through changes in long-term potentiation (LTP) and long-term depression (LTD), which are plasticity processes respectively strengthening or weakening synapses connections. Four studies reported decreases in LTP upon exposure to acute restraint stress at PND14-28, PND28-30, PND21-28 and PND30 [70–73], whereas one study reported increases in LTP upon exposure to chronic social isolation at PND22-50 [74]. Three of these studies also observed increases in LTD in presence of acute restraint stress (PND14-28, PND21-28, PND33-37) [70, 73, 75]. Interestingly, changes in LTP and LTD were reversed by treatment, during the stress challenge, with the antidepressant-like compounds capsaicin [70], an agonist of the transient receptor potential vanilloid subtype (TRPV1), and Ro25-6981 [73], an inhibitor of the glutamate N-methyl-D-aspartate (NMDA) receptor GluN2B subunit. Moreover, impairments in learning and recognition were present [70, 73], and were reversed by capsaicin and the GluN2B subunit inhibitor [70, 73]. Overall, studies demonstrate dysfunctions in LTP and LTD in

248 adolescence, after stress, and highlight the potential of pharmacological interventions to
249 reverse these together with memory impairments.
250
251 In six studies, dendritic formation, density and morphology were also generally
252 disrupted during adolescent stress. A marker of dendrite formation, spinophilin, was increased
253 in males after stress, but decreased in females upon exposure to social isolation at PND30-
254 35, however there was an increase in depressive-like behaviours in both males and females
255 [76]. Along with this, four studies reported that stress reduced dendritic spine density and
256 detrimentally affected morphology (length and size) upon exposure to social defeat stress
257 (PND35-44), chronic restraint stress (PND20-41, PND21-35, PND21-28) [58, 73, 77, 78].
258 These changes were accompanied with memory deficits and depressive-like behaviours [73,
259 77]. In contrast, stress increased the volume of a hippocampal subregion, the CA1, in one
260 study upon exposure to chronic physical stress (PND28-55) [79], but decreased volume of
261 mossy fibres, the projections between the dentate gyrus and CA3 regions of the hippocampus,
262 especially in animals that were more sensitive to chronic variable physical stress (PND28-41)
263 [79, 80]. All of these changes were accompanied by deficits in memory, as well as increased
264 depressive-like behaviour [79, 80]. Thus, deficits in dendrite formation and changes in their
265 density and morphology appear to be associated with memory dysfunctions and depressive-
266 like behaviour.
267
268 Ten studies investigated changes in the protein or gene expression of brain-derived
269 neurotrophic factor (BDNF), a protein highly involved in promoting cell proliferation, survival
270 and growth. Six out of these studies reported increases in BDNF upon exposure to chronic
271 cortisol treatment (PND29-49) and physical stress (PND28-41), acute restraint stress
272 (PND38), and social defeat stress (PND45-46) [62, 66, 74, 80, 81], two showed decreases
273 upon social instability stress (PND30-45) and social isolation (PND30-60) [82, 83], and the
274 remaining two showed no differences upon exposure to crowding (PND28), restraint stress
275 (PND31-38) and CMS (PND45-60) [84, 85]. In terms of cognition and behaviour, while some

studies showed either no changes or increased in BDNF levels, they still reported cognitive impairments and an increase in depressive-like behaviour [82, 84, 85]. However, two other studies found that increased BDNF after stress was associated with better memory performance [62, 81]. Moreover, another study found a reduction in BDNF associated with a disruption in cognitive performance, and increased depressive-like behaviours, which in this case were reversed by supplementing animals with an omega-3 fatty acids and vitamin A diet during the stress challenge (PND30-45) [83]. These findings therefore suggest dietary interventions could be valuable strategies to reverse stress-induced detrimental changes in neuroplasticity, cognitive function and behaviour.

Adulthood

Changes in hippocampal neurogenesis, hippocampal-dependent cognitive function and behavioural outcomes

Two of the aforementioned studies assessed neurogenesis outcomes in young adulthood after adolescence stress exposure [48, 53]. The first one showed that reductions in proliferation measured with non-co-labelled BrdU, as well as depressive-like behaviour, observed at PND47 after social instability stress (PND28-46) were no longerpresent at PND67 after a period of rest (PND43-66) [48]. Similarly, the second study showed that the initial increase in proliferation, measured with non-co-labelled Ki67 and observed at PND33 upon exposure to social instability stress (PND30-45), did not last over time and was not present at PND74-75, although these animals developed spatial memory impairments [53]. Adult neurogenesis has been associated with both increased memory and forgetting [21]. Together, these studies confirm that stress during adolescence can decrease cell proliferation close to the exposure, but not over time, and that after a period of non-exposure, neurogenesis can be restored and depressive-like behaviour disappear, at least in resilient subjects.

Changes in neuroplasticity, and hippocampal-dependent cognitive and behavioural outcomes

Out of the aforementioned studies, five of them assessed neuroplasticity outcomes over time, with measurements in adulthood [53, 62, 65, 79, 83]. The first study reported that levels of the neuroplasticity marker PSD95, which were unchanged after adolescent stress with cortisol at PND51, remained the same at PND78 [62]. The second study observed increases in the expression of the plasticity marker PSA-NCAM at PND90, which was not previously present during adolescence, upon exposure to peripubertal stress (PND28-42) [65]. However, two other studies found that dendritic spine density [78] and the volume of the hippocampal subregion CA1 [79] decreased over time after respectively, adolescent restraint stress (PND21-35) and chronic physical stress (PND28-55), when comparing PND56 with PND76 [79], and PND38 with PND68 timepoints [78]. Similarly, reduced BDNF levels were found to either normalise or remain decreased into adulthood at PND78 [62], and PND70 [83], after adolescent exposure to respectively cortisol (PND29-49) [74] and social instability stress (PND30-45) [83]. With regards to cognitive function and behavioural outcomes, memory impairments and depressive-like behaviours either persisted or developed during adulthood [53, 65, 79, 82, 83], although these could be prevented by omega-3 fatty acids and vitamin A dietary supplements administered since adolescence (PND30-75) [83]. Together, these studies indicate that detrimental effects on neuroplasticity, cognitive functions and behaviour can either persist or develop in adulthood as a consequence of stress exposure during adolescence, but indicate benefits from nutritional interventions in preventing persistent effects.

DISCUSSION

In this review we provided the first *systematic* summary of the available literature investigating changes in hippocampal neurogenesis, neuroplasticity and hippocampal-dependent cognitive and behavioural outcomes in adolescent animals exposed to stress-induced models of depression, and examining the same outcomes long-term into adulthood. Overall results show a significant reduction in hippocampal cell proliferation, associated with

an increase in depressive-like behaviours in animals exposed to stress challenges, however reduction in the number of surviving new-born neurons was not accompanied by changes in cognition and behaviour. In addition, studies observed alterations in neuroplasticity, including a decrease in pre- and post-synaptic markers, dendritic spine length and density, and in synaptic potential. Changes in neuroplasticity were accompanied by cognitive impairments, such as a decrease in learning and memory, and by an increase in depressive-like behaviours. Overall, some of the neuroplasticity effects of stress observed during adolescence either worsened or persisted during adulthood, especially when looking at cell proliferation, cognition and depressive-like behaviour. Interestingly, treatment during adolescence with antidepressants, glutamate receptor inhibitors, GR antagonists, or a healthy diet, consisting for example of omega-3 fatty acids and vitamin A, were able to reverse or prevent these detrimental changes.

First of all, results show a significant reduction in hippocampal cell proliferation and a concomitant increase in depressive-like behaviours in adolescent animals, upon exposure to stress challenges. In particular, animals exposed to stress between PND24 and PND49 showed a significant lower number of non-co-labelled BrdU positive proliferating cells within the hippocampus [46–50] (Figure 2). This was independent of the type of stress (social defeat, social instability, or cortisol administration), duration of stress (acute or chronic), as well as time of brain tissue collection (immediately after the stress challenge up to 12 days after). Moreover, among the aforementioned studies, three measured behavioural changes and two found an increase in depressive-like behaviour [48, 50], whereas one did not observe any change [49]. In this case, the reason could be due to the use of a different stress challenge, respectively, social instability [48] or cortisol treatment [50] vs social defeat stress [49], as well as the behavioural test being performed immediately after the challenge [48, 50] rather than a day after the end of the stress challenge [49]. This could suggest that, in contrast with cell proliferation, behavioural outcomes are dependent on the type of stress as well as time of behavioural testing.

However, in contrast with previous results, three studies found either a decrease, increase or no effect on cell proliferation, in this case measured with the marker Ki67, and no changes in cognitive function or depressive-like behaviour [46, 49, 53]. What is interesting to note is that although two of these studies exposed animals to the same type of stressor (social instability) and for the same duration (PND30-45), the first found no changes, whereas the second study found an increase in Ki67 positive cells [46, 53]. One reason for this could be due to the fact that BrdU is incorporated only during DNA replication, while KI67 is expressed at any time of mitosis except G0. The decrease in proliferation was only observed in tissue collected at PND33, but not at PND46 [46, 53], suggesting the deficit may occur only early on, close to the exposure. To confirm this, in the third study measuring Ki67 at PND35 the authors found instead a decrease in proliferation [49]. Timing of tissue collection from the stress exposure plays a significant role on findings related to proliferation (or Ki67), while Ki67 expression increases immediately after stress (at PND33), it decreases over time during the adolescent period (PND35 onwards), ultimately reaching a plateau [49]. Accordingly, this may explain why immediately after stress (PND35-49) there were no changes neither in cognitive function nor in depressive-like behaviours [46, 49, 53].

Studies also observed a reduction in the number of new born neuron survival, identified with the marker NeuN co-labelled with BrdU [49, 51], but inconclusive findings for changes in the number of neuroblasts or immature neurons, in this case detected with the marker DCX [2, 47, 53–56] (Figure 2). On this respect, it is interesting to note that while two studies showed a decrease in DCX positive cells [47, 54], two other studies found the opposite [53, 55]. One of the reasons for these contrasting outcomes could be the use of different stress types and durations: biological and/or acute stress challenge (IL1β injection, at PND28; social defeat stress, at PND30) [47, 54], versus behavioural and CMS challenges (social instability, PDN30-45; chronic mild stress, PND28-42) [53, 55]. In the acute immune challenge the number of DCX immature neurons decreased [47, 54], whereas the opposite was observed when using chronic behavioural stress challenge [53, 55]. This is indeed confirmed by our *in vitro*

388 experiments where we showed that exposing human hippocampal progenitor cells to an acute
389 immune challenge with the same cytokine IL1β can dramatically reduce the number of
390 immature neurons [35]. Therefore, neurogenesis, and especially the number of immature
391 neurons can be differentially affected by a stressful insult, used here as a model of depression,
392 and this can very much depend on both the duration and type of insult. Furthermore, some of
393 the studies measuring DCX and BrdU/NeuN positive cells also investigated hippocampal-
394 dependent cognitive function and depressive-like behaviours, but did not observe any
395 modifications [49, 50, 53, 54, 56]. However, this evidence comes from a relatively low number
396 of studies, and therefore makes it difficult to draw any significant conclusion.
397
398 Studies also observed negative changes of markers of neuroplasticity, including a
399 decrease in markers of pre- and post-synaptic plasticity, respectively synaptophysin [60] and
400 PSD95 [58–60], decrease dendritic spine density [58, 73, 77, 78], and synaptic potential [70–
401 73, 75]. Most importantly, changes in neuroplasticity were accompanied by cognitive
402 impairments, such as a decrease in learning and memory [70, 73], whereas changes in
403 synaptophysin and PSD95 were accompanied by an increase in depressive-like behaviours
404 [59, 60] (Figure 2). In particular, impairments in object recognition and spatial memory were
405 observed immediately after the last day of stress, independently of whether animals were
406 exposed to either an acute [70] or chronic stress challenge [73]. Similarly, the effect of stress
407 on synaptophysin, PSD95, and depressive-like behaviours were independent of the type of
408 stress challenge used, either biological or psychological (cortisol or CMS) [59, 60]. However,
409 in this case the challenge was applied only chronically (PND29-49, PND28-61) [59, 60],
410 therefore future investigations are required in order to understand whether an acute challenge
411 is also able to cause similar effects on both neuroplasticity and behaviours in these animals
412 during adolescence.
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Of interest, some of the effects observed by the studies during adolescence either worsened or persisted during adulthood, especially when looking at levels of proliferating cells, again identified with the marker Ki67 [53], or with other markers of neuroplasticity, like dendritic spine density [78] and hippocampal volume [79] or the neurotrophic factor BDNF [82, 83] (Figure 2). In particular, those studies which observed an increase in Ki67 (at PND33) and hippocampal volume (at PND56) during adolescence upon exposure to respectively, social instability or chronic physical stress, found instead a reduction in Ki67 and hippocampal volume during adulthood (Ki67 at PND74-75; hippocampal volume at PND76) [53, 79]. Similarly, another study, which observed a decrease in BDNF levels during adolescence (at PND50) found these levels to remain decreased also during adulthood (at PND70) [83]. Together with BDNF, impairments in object recognition memory and depressive-like behaviours, which were previously observed during adolescence, remained negatively affected as well during adulthood [83]. Overall, these findings are very precious as so far only a limited number of studies have examined changes in neurogenesis, cognition, and behaviour during adolescence in models of depression, as well as their persistence later in life. Of note, these results correspond to findings in humans, which show that cancer treatment in children and adolescents with brain radiation, which ablates hippocampus neurogenesis [86, 87], produces long-term cognitive impairments along with cognitive impairments and depressive symptoms [88]. This is of fundamental importance as it proposes adolescence as a perfect time for therapeutic interventions.

Of particular interest is that treatment during adolescence with either antidepressants, glutamate receptor inhibitors or GR antagonists reversed the detrimental effect of stress previously observed on neuronal survival (NeuN), neuroplasticity (LTP), and cognition [49, 51, 73] (Figure 2). Of note, this was independent of the type of stress, duration of stress, or type and duration of pharmacological treatment [49, 51, 73]. In line with these findings, extensive evidence has demonstrated that functional hippocampal neurogenesis is necessary for antidepressants to exert their beneficial properties on both cognition and behaviour [39, 89,

90]. In particular, the time course of maturation of newly generated neurons in the DG, which is generally consistent with the delayed onset of therapeutic action of antidepressants, and the unique physiological properties (plasticity and excitability) of adult-born dentate granule neurons qualify adult hippocampal neurogenesis as a fundamental antidepressant target [39, 89, 90]. At present, one neurogenic and neurotrophic compound called NSI-189 phosphate (NSI-189), whose antidepressant activity is monoamine-independent, has been tested in adult patients with depression (phase 2b trial). Results showed significant improvements in cognitive function and a reduction in depressive symptoms after 12 weeks of oral treatment [91]. These findings are quite interesting and propose pharmacological compounds targeting neurogenesis as valid alternative therapeutic approaches for patients with depression experiencing neurogenic and cognitive alterations.

In addition to pharmacological treatments, nutritional intervention with omega-3 fatty acids and vitamin A since adolescence (PND30 onwards), reversed the decrease in levels of BDNF, as well as cognitive impairments and depressive-like behaviours, previously observed during adolescence (at PND50), but also prevented their persistence during adulthood (at PND70) [83]. Accordingly, previous studies have shown that consumption of diets rich in omega-3, vitamin A or vitamin E are able to induce an increase in the levels of hippocampal neurogenesis and hippocampal volume, and reduce depressive symptoms, respectively in adult animals [92, 93] and humans [94–96]. However, at present, studies investigating the effect of these interventions, especially non-pharmacological, on neurogenesis during adolescence are relatively limited. Further investigations will be of fundamental importance to understand what are the exact neurogenic mechanisms through which they work in adolescent animals and, as a consequence, how they can be best used as therapeutic strategies in adolescent humans where putatively similar mechanisms are compromised.

So far hippocampal neurogenesis, both in adolescence and adulthood, has been mainly investigated at a *cellular level*, using either histological analyses of hippocampi isolated

from animal tissue [14, 20, 57, 97], or, more rarely, from post-mortem human brain tissue [14, 20, 57]. However, more recently, advancements have been made in the field, throughthe use of neuroimaging tools as a new way to measure this process in living humans. Neuroimaging methods, such as Blood Oxygenation Level Dependent-functional MRI, Cerebral Blood Volume and Magnetic Resonance Spectroscopy can be used to relate the putative adult neurogenesis-mediated changes to behaviour, including for aspects of memory and emotion, known to be altered by adult neurogenesis in animal models of depression [98, 99]. However, a major limitation of *in vivo* neuroimaging investigations is the difficulty in ascribing observed imaging effects to cellular and molecular changes. As such, animal studies of parallel design are still required in order to assess direct measures of adult neurogenesis which can be linked with neuroimaging outcomes [98, 99]. While at present valid imaging studies assessing hippocampal neurogenesis in adolescents are absent, and very limited in adult humans [98, 99], pre-clinical evidence investigating neurogenesis in adolescent animals is promising, as demonstrated in this review, and will provide significance cellular and molecular insights, as well as guidance for future neuroimaging investigations in this specific sub-group of individuals.

Although this review has limitations due to the relatively limited number of studies, the variety of models and the numerous molecules, as well as cognitive and behavioural testing that were performed, this is the first attempt at conducting a *systematic* review summarising changes in hippocampal neurogenesis, neuroplasticity, and hippocampal-dependent cognitive function and behavioural outcomes in adolescent animals exposed to stress models of depression, and also investigating long-term changes in the same outcomes during adulthood. Such a comprehensive insight into the holistic effects of neurogenesis is necessary to uncover and translate its potential as a therapeutic target for patients experiencing adolescent depression. While more animal research is still needed to fully ascertain whether there is a causal relationship between reduced neurogenesis, induced by a stress challenge, and increased depressive-like behaviours, it is important to note that the majority of the studies

included in this review which reported detrimental changes in neurogenic and/or neuroplasticity markers also found an increase in depressive-like behaviours [50, 58–60, 77, 82, 83]. Of note, while depressive behaviours in animals are not fully comparable with human depressive symptoms, they still reliably recapitulate some aspects of the depressive phenotype often observed in depressed individuals.

Finally, while testing causal interaction between neurogenesis and behaviour, additional focus should be given to the molecular mechanisms underlying such neurogenic and behavioural modifications, especially when considering type and duration of the stressful challenges. Also, further examinations of sex differences are required. The majority of the studies conducted so far, and included in this review, performed experiments mainly in male animals, which therefore did not allow us to draw any conclusions on this respect. In addition, some of the studies included in this review showed high risk of bias as they did not extensively describe the experimental methodologies which were followed, for example whether they did blinding or randomisation, therefore suggesting the need of more methodological details from future investigations.

CONCLUSION AND FUTURE DIRECTIONS

In conclusion, this is the first *systematic* review reporting detrimental changes in neuronal survival, neuroplasticity, and in hippocampal-dependent cognitive function and behavioural outcomes in animal models of adolescent depression. In addition, our review shows that some of these cellular, cognitive and behavioural changes can have long-lasting effects until adulthood, and that intervention with antidepressants or a healthy diet can reverse or prevent these modifications. While studies discussed in this review are promising, much work is still needed to fully elucidate the immediate and long-term impact of these changes, and the role of antidepressants and dietary interventions as effective treatment strategies, especially in humans. In the future, novel neuroimaging tools should be developed as a more direct way to measure hippocampal neurogenesis in living humans, ultimately bridging the gap

between animal and clinical findings, and contributing to the development of novel and more effective treatment approaches targeting hippocampal neurogenesis for adolescents with depression.

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Conflict of Interest

The authors declare no conflict of interest.

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Figure Caption:

Figure 1. Parallellelism between human and rodent lifetime development, depicting the adolescence period in humans corresponding on average to the period between postnatal days (PND) 21 to 65 in animals.

Figure 2. Effects of stress on neurogenesis, neuroplasticity, cognitive function and depressive-like behaviours in adolescence and adulthood, and examples of interventions able to reverse or prevent these effects.

Table 1. Neurogenic, neuroplasticity, cognitive and behavioural outcomes of pre-clinical studies.