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Review

Effects of environmental enrichment and voluntary exercise on neurogenesis, learning and memory, and pattern separation: BDNF as a critical variable?

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ABSTRACT

Adult-generated neurons in the dentate gyrus of the hippocampus have been the focus of many studies concerned with learning and memory (L&M). It has been shown that procedures like environmental enrichment (EE) or voluntary physical exercise (Vex) can increase neurogenesis (NG) and also enhance L&M. It is tempting to conclude that improvements in L&M are due to the increased NG; that is, a causal relationship exists between enhancement of NG and enhancement of L&M. However, it remains unclear whether the L&M enhancement observed after these treatments is causally dependent on the increase in newborn neurons in the dentate gyrus. It remains a possibility that some unspecified change – a "third variable" – brought about by EE and/or Vex could be a causal determinant of both NG and L&M. We suggest that this third variable could be neurotrophic and/or plasticity-related factors such as BDNF. Indeed, both EE and Vex can induce expression of such proteins, and BDNF in particular has long been linked with L&M. In addition, we argue that a very likely source of variation in previous experiments was the load on "pattern separation", a process that keeps similar memories distinct, and in which NG has been shown to be critically involved. To attempt to bring these ideas together, we present preliminary evidence that BDNF is also required for pattern separation, which strengthens the case for BDNF as a candidate third variable. Other ways in which BDNF might be involved are also discussed.

Contents

1. Effects of environmental enrichment and physical exercise on neurogenesis and learning and memory

The adult brain produces new neurons in substantial numbers, a phenomenon that has been firmly established since its initial discovery [1,2]. Of particular interest to researchers interested in the neurobiology of L&M are the newborn granule neurons in the hippocampus. These cells functionally integrate into the hippocampal dentate gyrus (DG) network [3], and receive synaptic input from the entorhinal cortex and form functional terminals onto CA3 cells [4,5]. In addition, adult-born neurons have been found to be relatively more excitable than mature granule cells [6,7], leading to the suggestion that these neurons may carry out a unique computational function within the DG [8,9]. Recently, the idea that adult-born neurons may play a special role in L&M has attracted considerable attention [10–12]. The amount of adult NG can be significantly altered by a number of factors in the external and internal environment, including neuronal activity, ageing, exposure to stress, epileptic insult and the focus of the current review, environmental enrichment (EE) and voluntary exercise (Vex) (for reviews see [13,14]).

Many studies have explored the relationship between EE, Vex, NG and L&M. EE usually involves exposure of animals to complex

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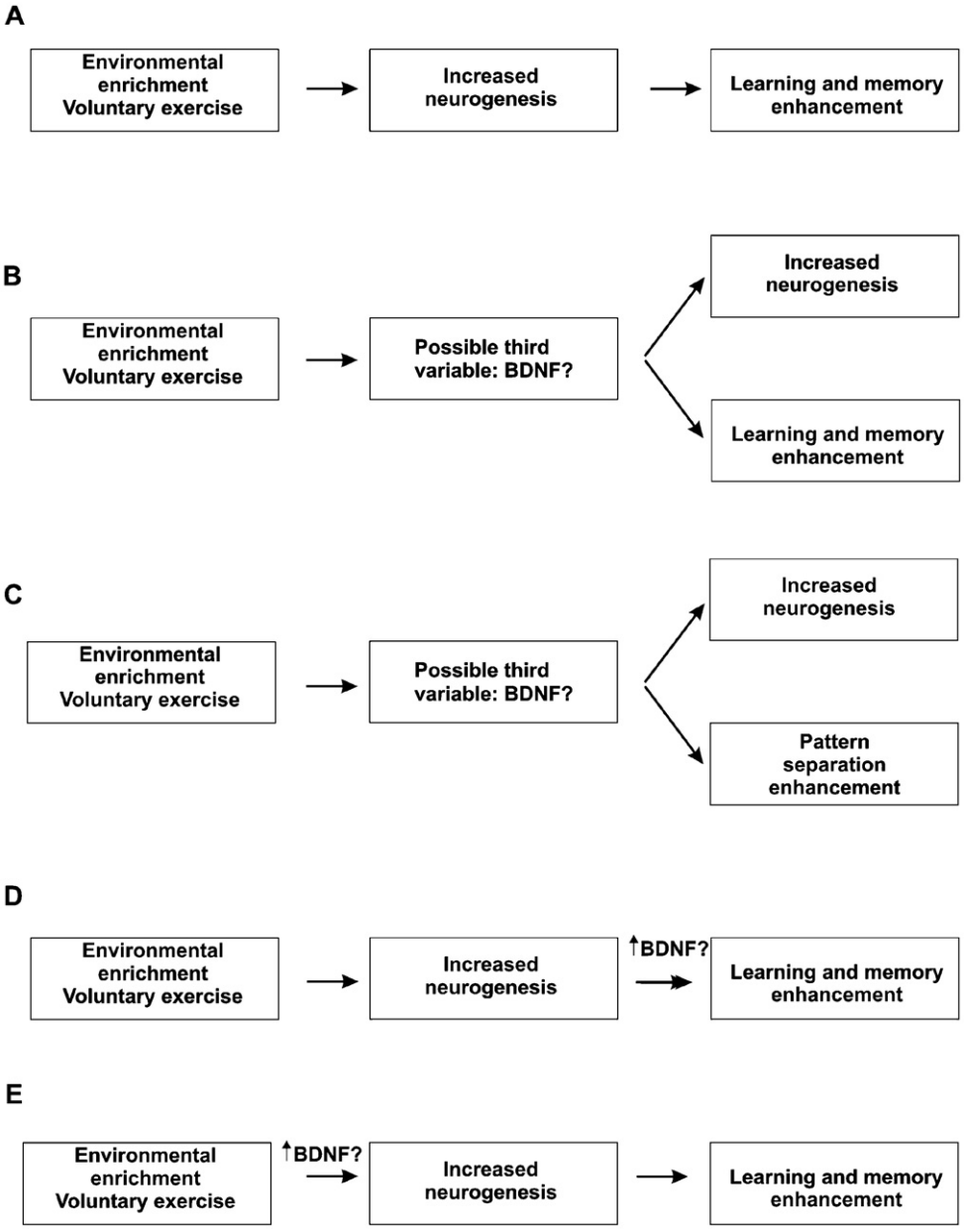

Fig. 1. Possible relationships between EE/Vex, NG, and L&M and some possible roles for BDNF. The figure depicts possible causal relationships only, and is not intended to represent the time-courses of action of BDNF, which can be either transient or long-lasting. (A) It is tempting to interpret experiments in which EE or Vex has been followed by an increase NG and also L&M as indicating a causal relationship between increased NG and enhanced L&M. However (B) it remains possible that some unspecified change – a "third variable" – brought about by EE and/or Vex could be a causal determinant of both NG and L&M. We suggest that such a third variable might be a neurotrophic and/or plasticity-related factor such as BDNF. (C) A modification of (B) to reflect the hypothesis that the EE/Vex experiments that found clear correlations with L&M were those in which the methods promoted a higher requirement for pattern separation. Thus insofar as this hypothesis is correct, in order to qualify as a candidate for a third variable, BDNF should be causally related to pattern separation. See text for discussion. (D) If the causal relationship shown in (A) turns out to be correct, one logical possibility is that immature neurons may secrete more BDNF than mature neurons, and it is this additional BDNF that would facilitate L&M directly. However, to our knowledge there exists little evidence for this hypothesis. (E) However there is evidence that BDNF may be able to induce NG.

environments that may include tunnels, nesting material and complex objects or toys and running wheels, and animals are often housed in larger groups to allow increased social interaction. Vex in most cases involves voluntary wheel running. It has been reported that both EE [15] and Vex [16] can increase adult NG, and that this increase is often paralleled by an improvement in performance on tests of L&M [17–21]. It should be noted, however, that new evidence is emerging suggesting that it may be the exercise component of EE which may be the critical factor in enhancement of NG (Henriette van Praag, personal communication). There have been numerous accounts of the positive effects of EE and Vex on L&M [15,22–26]. It is tempting to conclude that improvements in L&M are due to the increased NG; that is, a causal relationship is assumed between increased NG and the enhanced L&M (as depicted in Fig. 1A).

2. Correlation, causation, and the problem of the third variable

As discussed previously, there is much evidence to demonstrate that both EE and Vex can increase NG in the adult hippocampus. However, whether the beneficial effects of EE and Vex on L&M are

caused directly by NG, remains unclear. One obvious problem is that correlation does not imply causation. One alternative interpretation of the finding that NG correlates with EE or Vex is that, rather than increases in NG being causally related to improvements in L&M, there may be a "third variable" caused by EE or Vex that mediates both NG and L&M (see Fig. 1B). For example, EE and Vex can be accompanied by physiological and structural changes in brain regions including the hippocampus. EE, for example, was shown to increase total granule cell number [15], alter dendritic complexity and spine density and increase vascularization in the hippocampus [27,28]. Any of these changes could potentially contribute to the observed changes in cognition.

Ideally, experiments designed to explore a causal link between increased NG and better L&M would combine EE and Vex with selective blockade of potential increases in NG. If NG and L&M are causally linked, then although EE or Vex will lead to improvements in L&M under normal circumstances, they will not do so in conditions under which NG is prevented. Such experiments have indeed been carried out – to our knowledge there are at least five such studies – but unfortunately, taken together the results are inconsistent. In one such study, Meshi and collaborators combined X-ray focal irradiation with EE in mice and, although irradiation successfully blocked the EE-dependent increase in NG, it did not prevent the enhancement in learning or memory retention in the Morris water maze [29]. In another study, Bruel-Jungerman and collaborators found that EE improved long-term object recognition memory and increased NG, and that methylazoxymethanol acetate (MAM) treatment applied during the EE period completely prevented both the increased NG and the L&M enhancement [30]. MAM administration has widespread effects, however, and object recognition can be impaired by dysfunction in structures other than the hippocampus – indeed even more so (e.g. [31,32]). Wojtowicz and collaborators found a significant increase in the number of new neurons in the DG in runners compared to sitters; however, running did not enhance learning in the Morris water maze and only marginally improved contextual fear conditioning. In the same study, focal irradiation after Vex impaired contextual fear conditioning in both sitters and runners, but did not affect learning or performance in the Morris water maze, although a small impairment on reversal learning was found [33]. Using mice, Clark et al. found that running increased NG fourfold and in this case enhanced performance in both the Morris water maze and contextual fear conditioning tasks. Irradiation decreased NG by 50% in both runners and sitters and eliminated the gain in performance in the water maze, but did not prevent the enhancement of contextual fear conditioning [34]. Kitamura et al. [35] combined running and irradiation and examined contextual fear retention. The authors conclude that the running-induced enhancement in NG speeds up the decay rate of hippocampus dependency of memory; however this study was not designed to assess memory *enhancement* per se (indeed, neither running nor irradiation altered levels of freezing in control animals). The discrepancies between these studies could have been due to differences in the experimental methods, as will be discussed later. For now, the lack of a clear answer to the causality question leaves open the possibility that a third variable could exist in a causal relationship with both NG and the enhancement in L&M, leading to the correlations often seen between enhancements of NG and L&M seen following EE or Vex.[1]

[1] Indeed, adult neurogenesis can be significantly altered by a number of factors in the external and internal environment other than EE or Vex (as described above; for reviews, see [13,14]). The third variable problem also may apply to these phenomena, but for the purposes of this review, we focus on EE and Vex.

Because a third variable may exist, we can speculate what that third variable might be. Although there are a number of possibilities, some of which have already been mentioned above, we would like also to suggest the induction of neurotrophic and/or plasticity-related factors such as brain-derived neurotrophic factor (BDNF). The case is presented below, followed by some suggestions for experiments that could test this possibility.

3. Brain-derived neurotrophic factor (BDNF) as a possible third variable

Several lines of evidence provide a link between BDNF and L&M. First, BDNF has been found to play an important role in the late phase of long-term potentiation (LTP), the best known cellular plasticity phenomenon in the brain [36–38], which is thought to be one of the plastic phenomena that underlie L&M [39,40]. For example, Pang and others have shown that BDNF is necessary for the late phase of LTP (L-LTP) in the CA1 region of the hippocampus [41]. Second, BDNF mRNA and protein expression have been shown to be induced following learning [42–45]. Third, the effects of BDNF on structural plasticity are similar to those associated with learning. Hippocampus-dependent learning in particular has been associated with increases in the density of dendritic spines, synapse shape and receptor availability [46–48], and overexpression of BDNF in hippocampal slices can increase the number of dendritic spines in CA1 [49,50]. Similarly, BDNF overexpressing mice have increased dendritic complexity in the dentate gyrus (DG) [51].

Finally, and most convincingly, manipulations leading to BDNF or BDNF TrkB receptor dysfunction by global mutations or region-restricted manipulations have led to deficits in acquisition and consolidation of spatial information [52–56], avoidance learning [48,57–59], contextual fear conditioning [44] and object recognition memory [56,60]. In addition, exogenous application of human recombinant BDNF into the hippocampus enhances retention of inhibitory avoidance learning [58], memory persistence [61] and object recognition memory [62].

Indeed, it could be said that the causal evidence for a role for BDNF in L&M has been more consistent than that for NG and L&M. Although a large number of studies have been designed to investigate a causal relationship between NG and L&M, the results have not been unequivocal. In the review of Deng et al. [11], for example, fourteen studies are mentioned in which NG was ablated by agents such as MAM, irradiation or genetic tools and subsequent cognitive performance (on either the Morris Water maze or Barnes maze) was examined [63,64]. Of these fourteen studies, eight did not find a deficit in the acquisition of a spatial learning task after ablation of NG [29,65–71], whereas five studies did find a deficit [72–76] and one study found no effect in the water maze, but a deficit in the Barnes maze [77]. Some of these studies also report memory performance, and three found no deficit on either short term and/or long term retention [29,67,71], whereas eight did [65,68–70,72,74–76]. Possible reasons for these inconsistencies are offered later in this review.

The foregoing discussion indicates that BDNF satisfies at least one criterion for a possible third variable: it is strongly – and causally – linked to L&M. Is there reason to think that BDNF could be a third variable in EE/Vex, NG and L&M experiments specifically? Both EE and Vex have been shown to increase the expression of BDNF in the hippocampus (left-most arrow in Fig. 1B) [26,78–82]. For example, Falkenberg and collaborators found increased BDNF mRNA in the rat hippocampus after EE that correlated with improved spatial memory [26] and Ickes and collaborators found increases in BDNF protein after EE in the hippocampus and cortex [80]. Rossi and collaborators found that environmentally enriched mice had 80% more BDNF protein in the hippocampus than mice

housed under standard conditions. Also, in a recent study, Kuzumaki and collaborators suggested that EE increases BDNF mRNA in the hippocampus of mice via sustained epigenetic modifications at the DNA level [83]. Vex has also been shown to induce BDNF. In their original paper [84], Neeper and collaborators measured BDNF mRNA after 0, 2, 4 or 7 nights of voluntary exercise and found a significant increase in the hippocampus that correlated positively with the distance run per night by each rat. In more recent work, Gomez-Pinilla and collaborators showed that blockade of BDNF activity in the hippocampus by infusion of a scavenger TrkB/IgG receptor counteracted the Vex-enhanced ability of rats to find the location of a hidden platform in a water maze probe trial [85]. They suggested that the capacity of exercise to enhance cognitive function is dependent on BDNF action in the hippocampus. In a correlational study, Griffin and collaborators [62] showed that intracerebroventricular administration of BDNF can mimic the enhancing effects of exercise on object recognition memory.

It is only possible to speculate about the mechanisms by which BDNF induced by Vex and/or EE might affect L&M. BDNF is thought to mediate changes in hippocampal synaptic plasticity [79], and so it seems plausible that Vex and/or EE-induced BDNF may affect L&M by mediating changes in neuronal plasticity. Vaynman and collaborators have identified several signal transduction pathways implicated in BDNF-mediated enhancement in L&M, all of them known to be important for several L&M tasks [79,86]. In particular, mitogen-activated protein kinase (MAPK) and calcium/calmodulin protein kinase II (CamKII) were found to be downstream effectors of BDNF action on gene expression associated with Vex [79]. Blockade of BDNF action during Vex was sufficient to abrogate the Vex-dependent enhancement in L&M and prevent both the Vex-induced increase in cAMP response element binding protein (CREB) mRNA and phosphorylation (activation) [79]. Importantly, CREB has been shown to regulate BDNF expression [87], a mechanism that may provide a self-perpetuating loop for BDNF action related to exercise. In addition, Vex has been found to regulate CREB expression via the MAPK and CamKII pathways [79]. Also, during Vex, CamKII has been shown to contribute to the BDNF-dependent regulation of synapsin I expression [79], a presynaptic protein that modulates vesicular release [88].

The foregoing discussion applies to Fig. 1B, which depicts a causal relationship between EE/Vex and BDNF (left-most arrow), and between BDNF and L&M (upper right arrow). There is also evidence to support the idea that BDNF is causally related to NG (lower right arrow). For example, infusion of recombinant BDNF into the DG stimulates NG [89] and riluzole-induced proliferation of granule cells in the DG was blocked by injection of an antibody against BDNF [90]. Also, heterozygous BDNF KO mice show decreased NG in the DG [91,92]. Nevertheless, very little is known regarding the mechanisms by which BDNF can alter NG. It is not even clear if Vex and EE increase NG through similar processes [93]. In one study, specific deletion of BDNF receptor TrkB in adult born neurons led to reduced long-term survival of these neurons and integration into hippocampal circuits [94]. However, in another study, ablation of TrkB in newborn cells impaired proliferation in the DG. TrkB in these cells was also shown to be required for the induction of proliferation by Vex [95]. Further experiments will be necessary to determine the mechanisms of BDNF-induced NG.

So, could NG following EE or Vex be just an epiphenomenon, due to the action of neurotrophic factors in the hippocampus that have a more direct effect on L&M? If so, then where does that leave NG? Does it have a role in L&M? As described above, experiments designed to investigate a putative causal link between NG and L&M have been inconsistent. As we discuss next, the answer may be that NG is required for a very specific cognitive function, which may have varied across those experiments.

3.1. Neurogenesis, BDNF and pattern separation

Although the search for a causal relationship between NG and a *general* L&M function has not yielded a consistent answer, it has recently been suggested that NG may be particularly important for a more specific process, that of *pattern separation*. Pattern separation refers to the computational process by which representations of similar input patterns are decorrelated, or made more distinct from each other. In this way, the brain might be able to keep distinct or less confusable memory representations of similar events. The DG specifically is thought to contribute to memory by functioning as a pattern separator [96].

The idea that the DG functions as a pattern separator stems from early computational modelling work, based on anatomy and physiology, in which it was argued that the recurrent connectivity within the CA3 subregion of the hippocampus is ideally suited to storage of episodic memories [97]. Subsequent work in this area indicated that such a recurrent network works perfectly for orthogonal, or decorrelated, stored patterns, but breaks down with increasing similarity between patterns (e.g. [98–101]). Thus, for good performance, a recurrent memory network requires decorrelated inputs. Subsequent models therefore suggested that the sparse representations maintained in DG, combined with the anatomical properties of the projection from DG to CA3 [102] – in particular, the sparseness of the connectivity and the strength of the mossy fibre synapses – might be ideally suited to providing such orthogonal inputs to CA3 [99,103,104]. More recently, a number of models have considered whether there is a specific role for neurogenesis in pattern separation [8,105–108].

Recent behavioural experiments have provided evidence for a specific role for neurogenesis in pattern separation. Clelland and collaborators [109] used two ways to knock down NG in mice and found impairments in two very different behavioural tests of pattern separation. Compared to control mice, focally-irradiated mice or mice injected with a dominant negative Wnt-expressing lentivirus were impaired in a delayed nonmatching-to-place task in a radial maze, but only when they had to distinguish between arms that were close to each other. Irradiated mice were also worse than controls in a touchscreen location discrimination task, but again, only when these locations were close to each other and more easily confusable. Using the same touchscreen task, Creer and collaborators [110] showed that Vex enhanced performance, but only for the more difficult condition in which they had to rely more on pattern separation (however like the studies reviewed above, this study did not unequivocally demonstrate causality – although it was found that aged mice had impaired pattern separation and low neurogenesis that was refractory to running, showing that running alone does not necessarily lead to improvements in pattern separation). In a more recent study, Sahay and collaborators [111] found that genetically increasing NG might be sufficient to improve discrimination of similar contexts in a contextual fear discrimination task. In view of these new studies, perhaps the inconsistencies found in the less specific L&M experiments in which NG was knocked down could be explained in terms of variations in the requirement for pattern separation across different tasks, methods and apparatus. For example, variation in the discriminability of spatial cues used for the water and Barnes maze experiments, which can vary greatly between laboratories, would be expected to cause variation in the load on pattern separation processes. The same argument could be made for the inconsistencies found in the studies in which EE- or Vex-induced increases in NG were blocked, as different sets of spatial cues were most likely used for the water maze experiments and different training chambers were used for contextual fear conditioning.

We would like to return now to the issue of BDNF as a third variable. If we accept the story above regarding pattern

separation and NG, then it may be that the EE/Vex experiments that found clear correlations with L&M were those in which the methods promoted a higher requirement for pattern separation. In this case our diagram (Fig. 1B) needs to be modified to reflect this hypothesis. Fig. 1C thus shows that insofar as this idea is correct, in order to qualify as a candidate for a third variable, BDNF would need to be causally related to pattern separation. In this final section, we review recent experiments that show just that. Blockade of BDNF function by injecting BDNF-blocking antibodies directly into the DG impaired performance in a spontaneous location recognition task, but only when the animals had to disambiguate two similar locations within an open field, and not when these locations were made more dissimilar [112]. Moreover, preventing BDNF action in the DG impaired pattern separation only during the encoding/consolidation phase of the task – when pattern separation would be expected to take place – but not during retrieval. In addition, infusion of recombinant BDNF into the DG enhanced pattern separation when locations were made even more similar.

These findings raised the question of whether BDNF was equally released after exposure to similar or dissimilar stimuli, but was only *necessary* in the first case, or whether BDNF was expressed and released on an "as-needed" basis, that is, spontaneously in response to encountering similar events – the representations of which need to be separated before storage in memory. To test this, we exposed rats to two objects delineating either similar or dissimilar spatial locations within the open field and found a 4-fold increase in BDNF in the DG only after the rats explored two similar locations, but not after exploring dissimilar ones. These findings provide evidence that, perhaps surprisingly, BDNF appears to be expressed on an as-needed basis, that is, it is increased spontaneously in order to separate the representations of similar events.

What is the relationship between the Bekinschtein et al. [112] experiment and other experiments such as that of Clelland et al. [109], which show that both BNDF and neurogenesis knock-down can impair pattern separation? One possibility is that immature neurons secrete more BDNF than mature neurons, and that the impairment in Clelland et al. [109] was due primarily to reduction in number of those neurons, and therefore the decrease in the amount of available BDNF (this relationship is depicted in Fig. 1D). However there is not, to our knowledge, any strong evidence that immature neurons secrete more BDNF than mature neurons. This does not, however, exclude a role for immature neurons in BDNF-dependent pattern separation. Immature adult-born neurons have been shown to be more excitable than mature neurons and also to have enhanced plasticity [6,7], so these young granule cells may respond more rapidly to inputs of ambiguous spatial information in the DG. This enhanced response may be very sensitive to BDNF levels present in the hippocampus, which may activate TrkB receptors on young and/or adult neurons, thus strengthening the relevant connections. Indeed, it has been shown that ablation of TrkB in progenitor cells has a significant effect on behaviour [95], so acute blockade of BDNF could be particularly detrimental for these cells.

4. Concluding remarks

To summarise, we have suggested that in experiments investigating the link between EE, Vex, NG and L&M, there could exist a third variable, brought about by EE and/or Vex, acting as a causal determinant of both NG and L&M, and that this third variable could be a neurotrophic and/or plasticity-related factor such as BDNF. Of course this suggestion could be wrong; further appropriate experiments testing EE/Vex with NG knock-down and L&M (ideally examining pattern separation) may well generate unequivocal evidence that the causal relationships depicted in Fig. 1A are indeed correct. But where would it leave BDNF? Certainly it would no longer be needed as a third variable. It has already been stated that little evidence so far exists for the idea that immature neurons secrete more BDNF than mature neurons, and so the scheme in Fig. 1D is unlikely. BDNF would, however, likely still have other causal roles to play. Two ways BDNF might be involved is by acting on new neurons at the time of L&M testing, or at an earlier stage, by facilitating the NG that improves the L&M (see Fig. 1E; evidence for both of these possibilities has been described above). Thus we conclude by suggesting that whatever the outcome of investigations into EE, Vex, NG and L&M, BDNF is likely to have some role at some stage. Therefore, if one is interested in the molecules underlying NG and L&M, and pattern separation in particular, there may be no better place to start than with a molecule like BDNF.

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