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Author/s:
Pang, TY;Hannan, AJ;Lawrence, AJ

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Invited review

Enhancement of cognitive function in models of brain disease through environmental enrichment and physical activity

Terence Y.C. Pang*, Anthony J. Hannan*

Florey Neuroscience Institutes, Melbourne Brain Centre, University of Melbourne, Parkville, VIC 3010, Australia

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ABSTRACT

This review will provide an overview of the non-drug based approaches that have been demonstrated to enhance cognitive function of the compromised brain, primarily focussed on the two most widely adopted paradigms of environmental enrichment and enhanced physical exercise. Environmental enrichment involves the generation of novelty and complexity in animal housing conditions which facilitates enhanced sensory and cognitive stimulation as well as physical activity. In a wide variety of animal models of brain disorders, environmental enrichment and exercise have been found to have beneficial effects, including cognitive enhancement, delayed disease onset, enhanced cellular plasticity and associated molecular processes. Potential cellular and molecular mechanisms will also be discussed, which have relevance for the future development of 'enviromimetics', drugs which could mimic or enhance the beneficial effects of environmental stimulation.

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1. Introduction

The controversy and continual debate over the ethical implications of the use, and possible misuse, of cognitive enhancing drugs (such as methylphenidate) by healthy individuals appears to have overshadowed another group of potential beneficiaries. Those afflicted with pathological conditions that result in a compromise of cognitive ability, such as executive decision making and memory formation or recall, are clearly the key target population for such cognition enhancing drugs as a means of improving their quality of life. There is good evidence to support potential efficacy, with several drugs already in late-phase clinical trials as a means to delay or avert cognitive decline. However, these clinical assessments are more recent, with much of the current evidence of drug effects coming from animal studies. In comparison, non-drug interventions that improve cognitive ability in a healthy organism and also as a means of delaying cognitive decline and rescuing memory-related deficits in animal models of neurological conditions have been well-established to have significant beneficial effects.

Environmental factors which have been shown to enhance cognition in animal models include environmental enrichment, physical exercise and diet. Prior to discussion of environmental stimulation approaches in further detail, we will briefly outline the abundant evidence that a change in dietary environmental factors, namely nutritional intake and dietary supplementation of specific compounds, can have a significant impact on cognitive ability (see review by Gomez-Pinilla, 2008). A comprehensive discussion of diet-mediated enhancement of cognitive function warrants its own review and we recommend the expert review (XXXXX) in this issue for further reading. However, it is necessary to make mention of some of the dietary evidence in order to establish the most relevant

* Corresponding authors.
E-mail addresses: terence.pang@florey.edu.au (T.Y.C. Pang), anthony.hannan@florey.edu.au (A.J. Hannan).

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comparative behavioural and molecular indicators of enhanced cognitive function in rodent models.

It is well-established that omega-3 fatty acids are essential for brain function, with rodent studies reporting increased expression of a key neurotrophic factor, brain-derived neurotrophic factor (BDNF) in the cortex and hippocampus of rats provided dietary supplementation of omega-3 fatty acids (Vines et al., 2012). In contrast, a diet deficient in omega-3 fatty acids, especially during brain development, is associated with diminished capacity for neuronal plasticity and an emergence of anxiety-related behavioural changes (Bhatia et al., 2011). It might even result in greater susceptibility for addiction-related behaviours by causing an imbalance in key neurochemical signalling systems (McNamara et al., 2008).

Docosahexaenoic acid (DHA) is an omega-3 fatty acid crucial for the integrity of synaptic membranes. It has been shown to be involved in neuronal development and synaptic function (Cao et al., 2009), partly via its direct modulation of the voltage-gated Kv1.5 potassium channel (Koshida et al., 2009) for the maintenance of cell membrane potential. It is also involved in facilitating the movement of proteins crucial for vesicular release (Mazelova et al., 2009), and DHA-induced enhancement of neurotransmitter release (Mathieu et al., 2010) is one possible mechanism for its effect on synaptic signalling. DHA administration has been shown to effectively slow the development of memory deficits in the 3xTg-AD mouse model of Alzheimer's disease (AD) associated with minimising the loss of membrane area of neurons in the entorhinal cortex (Arsenault et al., 2011). In an alternative animal model of AD, Tg2576 transgenic mice, DHA supplementation improved learning and memory on the Morris water maze while preventing the loss of postsynaptic proteins (Calon et al., 2004). In a rat model of AD which develops learning deficits following infusion with beta-amyloid (1-40), pre-treatment with DHA improved avoidance learning in association with greater fluidity of synaptosomal plasma membrane (Hashimoto et al., 2006).

Given the importance of omega-3 fatty acids for a healthy structural composition of the cell membrane, there appears to be great potential for further investigation into the effectiveness of this combinatorial approach as a therapeutic option for neurological conditions that feature both neuronal loss and cognitive impairment. Other food-derived compounds have also been demonstrated to have cognitive enhancing effects. However, it has also been shown that inappropriate consumption of dietary supplements might have deleterious effects on cognitive function (Sumien et al., 2009). Due to space limitations, we refer the reader to other articles for a more in-depth discussion of this matter (Ramassamy, 2006, Kim et al., 2010, Howes and Perry, 2011).

Conversely, being overweight and obese associated with poor food consumption habits (and inadequate physical activity levels) are risk factors for lower cognitive performance, cognitive decline and dementia. There is an emerging field of clinical research to study the relationship between weight and cognitive functioning (see reviews by Burkhalter and Hillman, 2011, Elias et al., 2011, Siervo et al., 2011). The benefits of caloric restriction have been linked to a neuroendocrine response to low energy availability originating in the hypothalamus (Minor et al., 2009) and caloric restriction has also been demonstrated to counteract age-related hippocampal alterations in key synaptic proteins involved in neuronal signalling (Eckles-Smith et al., 2000, Fontan-Lozano et al., 2007, Shi et al., 2007) as well as DNA processing (Chouliaras et al., 2011). Caloric restriction has also been reported to up-regulate neurogenesis-related genes (the birth of new neurons is proposed to contribute to the encoding of new memories) in the hippocampus of a conditional double mutant mouse model of AD correlating with an improvement in novel object recognition performance and contextual fear conditioning memory (Wu et al., 2008b). The effects of caloric restriction extends beyond rodent models with a study of non-human primates demonstrating improved spatial working memory performances of grey mouse lemurs in a spontaneous alternation task and circular platform task (Dal-Pan et al., 2011), therefore the potential for clinical application certainly warrants further investigation. One aspect of caloric restriction is that it induces enhanced physical activity via weight loss and increased food-seeking behaviours, and the mechanisms involved may overlap with those of physical activity interventions, as discussed below.

2. Running has beneficial effects on cognitive performance

As the age-old adage goes 'Mens sana in corpore sano'. This quotation can be traced back to pre-Socratic times, and can be translated simply to mean 'A sound mind in a sound body'. While one might postulate that the beneficial effects of sound physical well-being were clearly exhibited during that period, the early philosophers could not have imagined that physical activity might be associated with improved cognitive function through its consequential effects on neural processes such as hippocampal neurogenesis (van Praag, 2008), brain angiogenesis (Kerr et al., 2010a) and increased expression of neurotrophic factors (Lista and Sorrentino, 2010). The effectiveness of physical activity to modulate cognitive function is well-described in the current scientific literature (Nithianantharajah and Hannan, 2009). In fact, the evidence supporting the cognitive benefits of exercise is so convincing that the collective findings from preclinical studies are being examined to identify potential molecular targets (some of which will be discussed below) for novel pharmacological interventions termed 'pharmacomimetics of exercise' (see review by Stranahan et al., 2009), which can be considered a subclass of 'enviromimetics' (see review by McOmish and Hannan, 2007).

2.1. Running delays cognitive decline associated with aging

The natural aging process is marked by impaired memory function and this is well accepted to be linked with a decline in hippocampal neurogenesis, although causal evidence of this relationship has yet to be uncovered. Also, while the age-related reduction of adult hippocampal neurogenesis is observed across several species (Gould et al., 1999, Amrein et al., 2011), it has yet to be definitively demonstrated in *Homo sapiens*. This was partly addressed by a study of the expression patterns of cell markers of neurogenesis that are routinely reported in rodent studies (Knoth et al., 2010). Despite the major caveat of assuming that humans and rodents share an expression profile of neurogenic markers, the study by Knoth et al. found similar quantitative age-related changes to markers of hippocampal neurogenesis in murine and human samples. MR imaging provides an alternative assessment of this process by demonstrating age-related volumetric reductions of the hippocampal formation (Apostolova et al., 2012) and in a randomised controlled trial of older adults, it was found that aerobic exercise training reversed age-related decline in hippocampal volumes and improved spatial memory (Erickson et al., 2011). This followed on from a previous randomised trial showing beneficial effects in older adults at risk of AD (Lautenschlager et al., 2008).

In rodents, functional neurogenesis in the hippocampus is well-established (van Praag et al., 2002), however the extent of age-related changes is also highly dependent on species and strain (Kuhn et al., 1996, Jucker et al., 2000, Lichtenwalner et al., 2001, Bondolfi et al., 2004, Epp et al., 2009). In mice, the expression profile of genes within the hippocampus changes with age but can be reversed by engagement in voluntary running (Kohman et al.,

2011; but also see Seki, 2002; Stranahan et al, 2010). This is a demonstration that the capacity for neuronal plasticity remains unaffected in the aged brain and physical activity, as a form of brain stimulation, results in physiological changes, enhanced hippocampal cell proliferation and neurite outgrowth (Wu et al., 2008a). *Bdnf* is one such gene that has its expression pattern inversely correlated with age. It has been reported that hippocampal levels of BDNF mRNA and protein decline with age but these deficits can be effectively ameliorated in mice that continuously engage in voluntary running (Adlard et al., 2005).

2.2. Running prevents cognitive deficits in a variety of Alzheimer's disease models

Age is the main influencing factor in late-onset Alzheimer's disease that is associated with the high risk ε4 allele of apolipoprotein E (APOE). Transgenic ε4 mice (the apoE4-TR line) expressing the human APOE4 protein variant have been reported to develop cognitive deficits on a variety of memory-related behavioural tasks (Grootendorst et al., 2005, Kornecook et al., 2010). However, when ε4 mice engaged in voluntary wheel-running for 6 weeks, impaired performance in the hippocampal-dependent radial-arm water maze task was rescued (Nichol et al., 2009), which suggested that despite the initial cognitive deficit associated with presence of the ε4 protein, the capacity for neuronal plasticity was still intact. It is likely that functional alterations in synaptic signalling are involved in this plasticity because of a specific up-regulation of synaptophysin, a presynaptic vesicular protein, in wheel-running transgenic ε4 mice. At a molecular level, an impact of running on neurotrophin signalling was also observed as it rescued a down-regulation of TrkB (the high affinity receptor of BDNF) protein in the hippocampus. MR imaging studies of aged ε4 transgenic mice, arguably a better representation of the human condition, have also confirmed progressive age-related reductions in hippocampal volume but these were detected after the onset of spatial learning deficits (Yin et al., 2011). However, it is widely acknowledged that the limits of current imaging technologies might not provide the precision required to detect subtle changes in hippocampal volumes within the intact mouse brain.

The robustness of the beneficial effect of exercise in AD is demonstrated by its consistent modification of cognitive impairment and disease markers in other models of AD. For instance, in the THY-Tau22 transgenic model of Alzheimer's-like disease, THY-Tau22 mice engaged in running showed normal (wild-type equivalent) preference for the novel arm in the Y-maze task in comparison to sedentary THY-Tau22 mice (Belarbi et al., 2011). The cognitive rescue was associated with a decrease in the level of abnormally phosphorylated Tau species in the hippocampus of running THY-Tau22 mice in a process likely to be linked with increased BDNF protein levels (Elliott et al., 2005). Interestingly, an up-regulation in mRNA levels of cholesterol trafficking-related genes was also detected, raising the potential for omega-3 fatty acid supplementation to also exert a benefit in this disease model.

The transgenic Tg2576 mouse model of AD develops plaque pathology associated with the induction of cytokines in the glial cells that surround the beta-amyloid (Aβ) plaques (Mehlhorn et al., 2000), and an altered immune response appears to be a mediator of cognitive impairment in this model (Sigurdsson et al., 2004). Interestingly, synaptophysin levels are maintained in this line with age (King and Arendash, 2002) despite a progressive development of cognitive impairment (Westerman et al., 2002). It remains unclear whether other presynaptic proteins are altered in this model, or if changes at the post-synaptic site are key to the cognitive deficits. Engagement in running improved the performance of Tg2576 transgenic mice on the novel object recognition task and radial-arm water maze (Parachikova et al., 2008, Yuede et al., 2009) while reducing the expression of proinflammatory markers in the brain (Nichol et al., 2008, Parachikova et al., 2008). It is worth noting that the novel location variation of the object recognition task has yet to be investigated in this model. Distinct brain regions have been implicated in the performance of both tasks despite their broad similarities (Ennaceur et al., 1997, Marois et al., 2000), so there is scope for future studies to investigate the effects of running on different brain regions and subtypes of cognitive function.

The triple-transgenic mouse model of AD (3xTg-AD) develops synaptic dysfunction and long-term potentiation (LTP) deficits which correlate with an intraneuronal build-up of Aβ (Oddo et al., 2003) resulting in cognitive deficits (Billings et al., 2005, Sterniczuk et al., 2010). Running is effective in ameliorating the progressive cognitive decline and the development of dementia-related behaviours in 3xTg-AD mice, with reduction in oxidative stress markers and a partial rescue of changes in LTP (Garcia-Mesa et al., 2011). In addition, the deficit in hippocampal neurogenesis is restored to levels similar to wild-type controls (Rodriguez et al., 2011) in a process likely to be BDNF-mediated (Blurton-Jones et al., 2009). What is more impressive is that this rescue of pathology in the study by Garcia-Mesa et al. was observed after the researchers provided the opportunity to engage in running to early symptomatic 3xTg-AD mice. Therefore, the results suggest that not only is running capable of delaying the disease process – it is potentially able to reverse it, at least at early stages. This remarkable result provides a glimmer of hope for sufferers of AD, especially those afflicted with early-onset AD who might still have the functional capacity to engage in relevant physical therapies.

In contrast, the APP-23 mouse model of AD has been found to be resistant to running-induced improvements in cognitive ability. Instead, the response to running was a down-regulation of hippocampal BDNF (Wolf et al., 2006). It is possible that the absence of a beneficial effect of running in this model could be due to inherent differences between the varieties of transgenic models of AD such as precise pathologies each are trying to model or even the background strain of the mouse line. However, it is also true that AD is a complex disease with a spectrum of potential underlying causes (genetic or environmental) and the challenge here is for researchers to pinpoint these differences and understand how these modifiers impact on the effectiveness of exercise as a therapeutic approach for AD.

Interestingly, a recent study reported that engaging in physical activity reduced the probability of cognitive decline for older individuals with the E4 allele but not for those without the E4 allele (Woodard et al., 2012). While future clinical studies will be required to confirm this finding, this does represent an important validation of the rodent studies and highlights their potential as preclinical models. It also raises the appealing prospect of a non-drug approach for delaying or even preventing the onset of AD symptoms for a subsection of the population at greatest genetic risk.

2.3. Limited evidence of running as a cognitive modifier of Parkinson's disease

In comparison to the number of studies of cognitive function in AD, there have been much fewer examinations of the potential disease modifying effects of physical activity on the development of cognitive impairment in Parkinson's disease (PD). The clinical evidence supporting a benefit of engaging physical activity associated with reduced risk of developing PD remains inconclusive (Thacker et al., 2008; Sasco, 1992) although a community-based randomised study examining Tango dancing reported improvements of Unified Parkinson's disease Rating scores of off-

medication patients (Duncan and Earhart, 2012). By comparison, the findings of a randomised controlled trial of training on a rotating treadmill based on the hypothesis that this would limit turning movement-related falls revealed limited short-term benefits (McNeely and Earhart, 2012) which was largely consistent with the findings of a meta-analysis that reported no significant effect of motor training on the risk ratio of falling incidence (Allen et al., 2011). However, a previous study had reported that employing six weeks of intensive treadmill training improved gait (Herman et al., 2007) thereby indicating that the period of therapeutic intervention is an important consideration for future studies aimed at assessing the efficacy of different treatment approaches. There are a surprisingly limited number of published rodent-based studies in this field. In a study using administration of reserpine – a monoamine depleting drug – as a pharmacological model of PD, it was found that at doses which did not induce any motor deficits, reserpine-treated rats displayed social memory deficits which were corrected by pre-exposure to 4 weeks of treadmill or wheel running (Aguiar et al., 2009).

Prior opportunity for voluntary running has also been demonstrated to be effective in reducing multiple parameters of PD-related pathology following administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) through mechanisms that involve a running-induced up-regulation of BDNF (Petzinger et al., 2007, Gerecke et al., 2010, Fredriksson et al., 2011, Wu et al., 2011). Similar neuroprotective effects of running have been reported in the 6-hydroxydopamine-induced rat model of PD (Yoon et al., 2007). However, a comprehensive investigation of the neuroprotective effects on cognitive function in these models has yet to be reported. The overall evidence of the neuroprotective molecular changes triggered in the PD brain by running supports its potential for correcting the cognitive deficits that could arise in the various rodent models of PD.

2.4. Running modulates cognitive deficits in Huntington's disease models

In comparison to AD and PD, rodent models of Huntington's disease (HD) have the advantage of being more consistent in their construct validity, i.e. expression of the *huntingtin* gene mutation encoding an expanded polyglutamine tract is sufficient to cause disease symptoms. Constant opportunity for voluntary wheel-running was demonstrated to delay the onset of hippocampal-dependant cognitive deficits in the R6/1 transgenic (human N-terminal fragment expressed via the *huntingtin* promoter) mouse model of HD (Pang et al., 2006). This running-induced behavioural benefit was concurrent with increased BDNF mRNA and protein expression in the hippocampus. The involvement of BDNF in modulating cognitive function in HD is further evident from a report that reducing BDNF expression in the R6/1 transgenic line resulted in accentuated cognitive impairment (Giralt et al., 2009). Despite consistent evidence that gene expression is disrupted across multiple brain regions in HD, it has been shown that running is capable of inducing a dramatic up-regulation of *Bdnf* gene expression in the hippocampus in transgenic HD mice (Zajac et al., 2010). Interestingly, the running-induced cognitive benefits were independent of a correction of the severe hippocampal neurogenesis deficits that is detected in the R6/1 line (Renoir et al., 2012b), a feature which has also been reported in the R6/2 transgenic line (Kohl et al., 2007). However, there is evidence that rather than neurogenesis, it is the rescue or preservation of hippocampal synaptic function that is crucial to running-induced cognitive recovery in HD. A study of two knock-in lines of HD mice (HdhQ92 and HdhQ111) demonstrated this by reporting that the application of BDNF was sufficient for rescuing deficits in LTP induction and consolidation in *in vitro* hippocampal slices (Lynch et al., 2007).

Interestingly, in another model of HD (N171-82Q transgenic mice, with expression of an N-terminal fragment driven by the *prion* promoter), the commencement of running from a presymptomatic age failed to confer any beneficial effects, and instead appeared to accelerate onset of disease symptoms (restricted to motor symptoms, the full cognitive assessment was not examined) (Potter et al., 2010). It should be noted that the mice were singly housed, and this social isolation could be one important difference from other running wheel studies in HD mice (Pang et al., 2006; van Dellen et al., 2008). However, despite the findings of that study, the collective evidence suggests that running is beneficial in HD models and rescues cognitive impairment, possibly through an up-regulation of the neurotrophin BDNF in the hippocampus. Due to the likelihood that motor symptoms would impede engagement in physical therapy, the development of compounds with the potential to mimic the molecular effects of environmental stimulation and physical activity ('enviromimetics'; McOmish and Hannan, 2007) would be ideal for treating the cognitive symptoms of this disease in the clinic.

2.5. Rodent models of chronic stress benefit from running

The effects of stress on cognitive functioning are well-studied. While the ill-effects of stress on memory are well-known, the interaction of stress and cognitive performance is a fine balance with some minimal level of stress required to actually facilitate memory formation. For example, acute psychosocial stress negatively impacts on emotional episodic long-term memory consolidation (Wolf, 2012) and impedes the implementation of flexible goal-directed behaviour (Plessow et al., 2012) but also serves a priming role in the enhancement of non-declarative memory (Hidalgo et al., 2012). In rodents, there are also distinct effects of acute stress on memory and hippocampal function. Acute stress from exposure to a novel context enhances the induction of CA1 hippocampal long-term potentiation and facilitates retrieval of fear memory (Motanis and Maroun, 2010), but disrupts paired pulse facilitation and long-term potentiation in the dorsal hippocampus (Cazakoff and Howland, 2010). In comparison, the detrimental effects of chronic stress on memory are more robust and consistent. Repeated exposure to restraint stress is commonly used to model chronic stress in rodents and induces molecular and cellular changes which are linked to the resulting cognitive dysfunction (Sousa et al., 2000, Venero et al., 2002, Pawlak et al., 2005, Nagata et al., 2009). There is stress-induced inhibition of hippocampal neurogenesis, however this can be attenuated by allowing the opportunity for voluntary wheel-running (Nakajima et al., 2010) and this is likely due to a running-associated protection against stress-induced decreased in hippocampal BDNF protein levels (Adlard and Cotman, 2004). The modulation of the physiological stress response following a period of running has been shown to be key to the exercise-associated improvement in spatial working memory in rodent models (Campeau et al., 2010). There is also an interesting interaction between stress and pre-existing conditions since stress accelerates the development of learning and memory impairments in a mouse model of AD (Jeong et al., 2006). While there is much to be learnt of the neuroprotective effects of running on stress-induced cognitive impairment, current evidence is supportive of its potential as a positive intervention.

2.6. Benefits of running in recovery from traumatic brain injury

Physical activity has also emerged as a potent neuroprotective against physical insults to the brain. Various approaches modelling

traumatic brain injury (TBI) in rats and mice consistently reproduce cognitive deficits associated with damage to the hippocampus (Hamm et al., 1993, Hicks et al., 1993, Wakade et al., 2010, Creed et al., 2011) and result in impaired performances on spatial memory tasks such as the Morris water maze and the radial-arm maze (Scheff et al., 1997, Skelton, 1998, Enomoto et al., 2005). Enhanced hippocampal neurogenesis has been linked with improved cognitive recovery after TBI (Kleindienst et al., 2005). One of the earliest studies of exercise as a therapeutic approach for recovery from TBI using fluid-percussion injury in rats found that the provision of exercise post-injury resulted in elevated expression levels of plasticity-related genes in the injured hippocampus including *Bdnf*, as well as improved cognitive performance in the Morris water maze (Griesbach et al., 2004). However, it is important to note that the precise time at which such an intervention was introduced significantly altered the prospect of recovery since rats that engaged in running during the first 6 days post-injury retained their cognitive deficits. Furthermore, a follow-up study examined the rate of running-induced recovery and found that the severity of the injury was also an important modifying factor (Griesbach et al., 2007). These findings are a strong indication that the acute and subsequent phases of TBI involve complex interactions of cellular and molecular changes which have yet to be fully understood. Exercise-related functional recovery is likely to involve the inhibition of neuronal cell death through a limitation of the impact of growth inhibitors at the site of injury such as the myelin-associated molecules MAG and Nogo-A (Chytrova et al., 2008, Itoh et al., 2011). More importantly, BDNF has been found to be essential for diminishing the inhibitory molecular signals resulting in functional recovery of cognitive capacity (Chytrova et al., 2008, Griesbach et al., 2009).

2.7. Cognitive impairment in addiction disorders – potential for exercise therapy?

Another form of external insult to the brain is the consumption or intake of substances with addictive properties. It had been reported that following an 8-week treadmill running program, rats that had undergone amphetamine-induced conditioned place preference showed preference away from the drug-associated compartment (Fontes-Ribeiro et al., 2011). While the engagement in the abuse of addictive compounds is more commonly associated with affective symptoms (Renoir et al., 2012a), there is also strong evidence of resulting pathology to the hippocampal formation. It would therefore not be surprising if cognitive impairment was indeed a robust and consistent feature of the numerous rodent models of substance abuse. However, the major challenge in demonstrating this in combination with a beneficial effect of exercise to correct those deficits would be accounting for any alterations in movement/exploratory patterns or even motivation to perform the cognition tasks by the rodent subjects. Much work is required to develop this field of investigation further.

2.8. Running + dietary supplementation of DHA

Additive effects of exercise and DHA dietary supplementation have been demonstrated (Chytrova et al., 2010). Voluntary running potentiated the effects of a 12-day DHA dietary supplementation on increasing hippocampal levels of synaptic proteins such as syntaxin 3 and the NMDA receptor subunit NR2B. The combinatorial molecular effects were translated into enhanced learning performance in the Morris water maze. The use of omega-3 fatty acid supplementation could be highly relevant for conditions that involve a deterioration of physical well-being which would limit any engagement of physical activity. Studies have found that dietary omega-3 fatty acids improve skeletal muscle blood-flow during exercise through increased cardiac output (Stebbins et al., 2010), thereby conferring a benefit on cognitive function, as well as physiological fitness. The prospect of greatly accelerating cognitive recovery in the various rodent models discussed so far is highly appealing and warrants further investigation.

3. Improvement of cognitive function through environmental enrichment

Environmental enrichment involves the manipulation of housing conditions to facilitate the enhancement of sensory, cognitive and physical activity. This enrichment can induce substantial changes to the developing and adult brain (van Praag et al., 2000, Sale et al., 2009). The effects of exposure to an enriched environment have been demonstrated to exert profound expression changes in genes linked to synaptic plasticity, neuronal signalling and learning and memory (Rampon et al., 2000). Environmental enrichment has also been shown to induce beneficial effects in a range of different animal models of brain disorders (Nithianantharajah and Hannan, 2006).

A discussion of cognition enhancement using mental stimulation-based materials and approaches is challenging because of the myriad of options that might be applicable to the individual. These could range from the use of a simple memory training task to improve a selective aspect of memory (e.g. for age-related memory deficits) to more complex behavioural therapy to re-learn social adaptation strategies (e.g. anorexia nervosa). Furthermore, certain conditions might be sensitive to the precise timing of when such therapy is put into effect (e.g. stroke; Poulin et al., 2012) and these require careful consideration on the part of the physician and therapist. For these various reasons, it has been difficult to develop specific cognitive-therapy protocols. However, that should not detract from evidence of the benefits of cognitive stimulation collected from studies of animal models using the paradigm of environmental enrichment as a means of correcting cognitive deficits. In this section of the article, we will review the demonstrated rescuing effects of cognitive enrichment in rodent models and discuss the potential therapeutic implications for particular disease conditions.

3.1. Aging-related cognitive impairment partially rescued by enrichment

Surprisingly, one could conclude that there is weak evidence for environmental enrichment having a significant benefit on cognitive impairment related to aging. However this could be attributable to a high degree of variance observed in the experimentation with aged animals (Bell et al., 2009), and of more concern, conflicting reports that rely on results from different behavioural tasks used. For example, Soffie et al., reported that old rats (23 months) housed for the duration of their life in enrichment conditions perform better on delayed sample to matching tests (Soffie et al., 1999). However, they had previously reported that similarly enriched old rats (22 months) did not exhibit any enrichment benefits in the Y-maze spontaneous alteration and spatial object recognition tasks (Van Waas and Soffie, 1996). One argument could be that the effects of environmental enrichment were not sufficiently robust for replication, however it should be noted that distinct brain regions have been implicated in the behavioural tests employed by both studies. The delayed sample to matching task in the 1999 study is a measure of short term working memory and MR imaging studies have demonstrated that it involves the activation of cortical regions (Habeck et al., 2005). (NB. Enrichment-induced plasticity has also been shown to extend to the visual system; Scali et al., 2012). In

comparison, the Y-maze and location recognition tasks involve a major spatial component and performance in these tests is highly dependent on hippocampal function. Therefore, researchers seeking to further examine the effects of enrichment on cognition need to design their studies carefully and only use test protocols which are specific for the type of cognitive parameter to be assessed and for the precise brain regions of interest.

Focussing on hippocampus-related cognition (learning and spatial memory), it has been demonstrated that aged rats perform worse in the Morris water maze and radial arm maze tasks (Bennett et al., 2006). Interestingly, a dose-related effect of enrichment was observed with aged rats exposed to 24-hours continuous enrichment outperforming those with 3-hours of daily enrichment on both spatial memory tasks. While the improvement in memory might imply improved hippocampal functioning, perhaps through an increase in neurogenesis, synaptophysin levels of enriched rats were lower than young and aged controls. This suggests that enrichment might possibly be rescuing the age-related spatial memory deficit through refinement of neuronal function rather than through an alteration of hippocampal cell turnover. Future work will be required to determine the processes involved in enrichment-mediated rescue, and to investigate whether these processes are modulated over time. The latter possibility is quite likely to hold true based on recent evidence that environmental enrichment as a therapeutic intervention against age-related cognitive decline has to be initiated before the median lifespan of the animal for there to be any beneficial effects (Freret et al., 2012).

It has been argued that the benefits of environmental enrichment paradigms are highly relative to the amount of physical activity that the animals engage in rather than the cognitive stimulation enrichment provides. This poses a major caveat for studies of aged animals (although it is reflective of the human population) since aged animals tend to explore and engage in physical activity less (Van Waas and Soffie, 1996, Valentinuzzi et al., 1997). However, with Kobilo and colleagues reporting that running is the main underlying intervention for enrichment-related neurogenic and neurotrophic stimulus in relation to improved hippocampal function (Kobilo et al., 2011), then any effect of environmental enrichment despite a decrease in physical movements provides indirect evidence for the benefits of cognitive stimulation on the aged brain.

3.2. *Varying effects of enrichment observed in models of Alzheimer's disease*

With memory deficits and dementia being significant features of Alzheimer's disease (AD), it is not surprising that the bulk of the published scientific literature regarding cognitive enhancement within the scope of any neurological conditions is associated with models of AD. This is consistent with numerous clinical studies exploring the effects of neuro-enhancing compounds in AD patients. But is pharmacotherapy the only viable option? What about cognitive therapy and what evidence is there from pre-clinical models?

Environmental enrichment has been reported to improve cognitive performance on a variety of tests including the Morris water maze, circular platform, platform recognition task and radial arm water maze (Arendash et al., 2004, Costa et al., 2007, Cracchiolo et al., 2007, Valero et al., 2011). Furthermore, those reports of enrichment improving cognitive output span several transgenic mouse models of AD (APPsw, PS1/DAPP, APPsw/PS1) thereby demonstrating the robust effects of this positive environmental intervention. However, subtle differences do emerge when we attempt to explain the effects of enrichment. A report based on work with the APP + PS1 transgenic line suggested a relationship between the beneficial effect of enrichment on cognitive function and a reduction in Aβ deposition (Cracchiolo et al., 2007). In contrast, in the APPsw model, a similar enrichment-associated improvement in cognitive function was not associated with a decrease in Aβ deposition across the brain (Arendash et al., 2004). These conflicting results might be indicative of differences in the pathological basis of these transgenic models, but could also be suggestive of restorative effects of enrichment that involve mechanisms that are independent and dependent on Aβ-related pathology.

To further complicate this discussion, the question of whether Aβ is an appropriate pathological measure that quantifies the effects of enrichment on the AD brain remains unresolved. The expectation that enrichment would exert beneficial effects in a manner that negatively correlates with Aβ deposition is based on the presumption that Aβ is a primary cause of neuronal dysfunction and cognitive impairment in the AD-afflicted brain. It was therefore somewhat surprising that a study by Jankowsky et al. reported an increase of Aβ deposition following environmental enrichment (Jankowsky et al., 2003). They postulated that the paradigm of enrichment constituted a form of stress on the mice but this pathological effect was later replicated by the same group with the additional observation of a rescue of cognitive impairment (Jankowsky et al., 2005). Therefore, this is a demonstration that quantification of Aβ load in transgenic models might not necessarily be the most appropriate biomarker for the assessment of effective therapeutic interventions in AD. However, both studies by Jankowsky et al. involved female APP/PS1 mice and the findings were in contrast to a similar study of male APP/PS1 mice by Lazarov et al. which reported a reduction of Aβ deposition attributable to an enrichment-associated increase in enzymatic activity of an Aβ-degrading endopeptidase, neprilysin (Lazarov et al., 2005).

Up-regulation of genes associated with neural plasticity and Aβ sequestration, and increased hippocampal neurogenesis, was also demonstrated in the brains of APP/PS1 male mice (Hu et al., 2010) but whether these correspond with an enrichment-mediated correction of cognitive impairment in these mice remains unknown. This potential correlation would be important to determine because of the existing controversy regarding the relationship of hippocampal neurogenesis to cognitive impairment in AD models. Reduced hippocampal neurogenesis has been demonstrated in different transgenic mouse models of AD and correspondingly rescued by enrichment (Herring et al., 2009, Valero et al., 2011) but there is also evidence of a contradictory increase in hippocampal cell proliferation and neurogenesis in APP/PS1 transgenic mice despite developing memory impairments (Yu et al., 2009). ApoE4 transgenic mice also have an unusual increase in hippocampal neurogenesis and environmental enrichment triggers apoptosis and decreases neurogenesis in this line of mice (Levi and Michaelson, 2007). Prior to resolving the exact involvement of altered hippocampal neurogenesis levels in the cognitive impairments of the various AD transgenic lines, one could speculate that measures of cognitive performance in these mice which have a strong hippocampal-dependent spatial component might in fact be subject to compensation from existing hippocampal connections. This is further evident from a combinatorial effect of enrichment and wheel-running on improving cognitive performance despite no change in the number of surviving new-born neurons in the hippocampus of APP/PS1 mice (Catlow et al., 2009). It is possible that enrichment evokes hippocampal plasticity that involves existing neurons for the encoding of new memory and enhanced performance on memory tasks (but see Sahay et al., 2011) and the prospect of being able to target and exploit existing neuronal networks warrants further investigation.

The variety of transgenic mouse models of AD mentioned in this article thus far are primarily models of familial AD. The AD11

transgenic mouse line expresses a recombinant anti-nerve growth factor (NGF) antibody and has progressive development of cognitive deficits and neurodegeneration akin to sporadic AD. Environmental enrichment has been found to modulate the development of the neuropathology by preventing the loss of choline acetyl transferase (ChAT) in the basal forebrain (but had no impact on accumulation of phosphotau in the entorhinal cortex), reducing Aβ burden in the hippocampus and eliminating the deficit in spatial learning on the Morris water maze (Berardi et al., 2007). The use of such mouse models are of particular importance to the AD research community since it is well-known that the vast majority of AD cases are sporadic.

Interestingly, the benefits of enrichment could partly be due to modification of peripheral physiology which in turn feedback in a positive manner onto brain function. In a study of 3xTg-AD mice, environmental enrichment starting from adulthood modified spleenic and thymic immuno-profiles, as well as maintaining fluctuations in plasma corticosterone levels (Arranz et al., 2011). Therefore, the cognitive enhancing effect of environmental enrichment could be mediated through a dual-process of promoting hippocampal plasticity in combination with regulation of peripheral 'anti-plasticity' systems such as activation of the immune system. There is clearly much to be learnt about the complex interaction between AD pathology and how the AD brain processes cognitive stimulation.

One of the molecular targets associated with neurodegeneration and cognitive impairment in Alzheimer's disease that has emerged as a target for cognitive enhancing interventions is the cyclin-dependent kinase 5 activator p25 which regulates neural development and synaptic plasticity (see reviews by Angelo et al., 2006, Su and Tsai, 2011). Previously, the generation of p25 had been proposed to be an indicator of neurotoxicity (Lee et al., 2000), a notion that was supported by findings from rodent studies wherein over-expression of p25 in neurons triggered neurodegeneration (Bian et al., 2002, Fischer et al., 2005). However, the link between p25 and cognition appears to be more complex because it was subsequently found that transient p25 expression or over-expression of lower levels of p25 in distinct brain regions results in enhanced synaptic plasticity and memory formation (Angelo et al., 2003, Fischer et al., 2005, Ris et al., 2005). By using a double transgenic mouse model with p25 expression under control of the *CamKII* promoter, Fischer and colleagues conducted a study that demonstrated the enhancement of hippocampal-dependent cognitive function by environmental enrichment (Fischer et al., 2007). Cognitive deficits in mice that were over-expressing p25 were effectively ameliorated by four weeks of housing in environmentally enriching conditions despite not rescuing the resulting neurodegeneration. Rather, enriched p25 over-expressing mice had increased levels of a variety of synaptic protein markers which suggested that the beneficial effects of enrichment evoked a modification of the synaptic network, perhaps by increasing the number of synaptic connections or dendritic complexity. Despite the strong indications of a positive effect of environmental enrichment, it is important to highlight that the environmental enrichment protocol adopted by the investigating group in this study included the provision of running-wheels. There is strong evidence that physical activity alone is sufficient to elicit changes in synaptic plasticity and levels of synaptic proteins (Tong et al., 2001, Vaynman et al., 2006, Lin et al., 2012), therefore further work will be required to differentiate between the effects of cognitive stimulation and physical activity on improving the cognitive ability of p25 over-expressing mice. However, the findings of this study are broadly consistent with a more recent report that the generation of p25 is in fact a core event that occurs during the formation of hippocampal-dependent spatial memories (Engmann et al., 2011). In that same study, analysis of post-mortem hippocampal samples from individuals with varying extents of tau pathology was undertaken and revealed that a marked reduction of p25 protein levels was present by early AD thereby refuting the original proposed neurotoxic role of p25 in AD pathology. This key finding further supports the potential of modulators of p25 activity as putative therapeutic options for addressing cognitive decline in AD.

The study by Fischer and colleagues also uncovered a potential molecular mechanism mediating the effects of environmental enrichment – chromatin remodelling through modification of histone proteins. By studying wild-type mice housed under environmentally enriching conditions, generalized increases in the acetylation levels of histone (H3 and H4) proteins were found in conjunction with improved learning performance. The extent of histone acetylation and its role in the regulation of associative memory was definitively demonstrated following administration of the histone deactylatase (HDAC) inhibitor sodium butryate which was sufficient to improve memory function. (For further evidence implicating HDAC regulation of cognitive function, see Guan et al., 2009). However, it is worth pointing out that physical activity alone has been reported to reduce HDAC activity (Elsner et al., 2011) therefore further work will be required to clarify and better understand the molecular mechanisms attributable to cognitive stimulation that is part of the broader environmental enrichment paradigm.

3.3. Enrichment and cognitive stimulation of HD transgenic mice improves spatial memory

Environmental enrichment in HD mice was the first demonstration of beneficial effects of this experimental manipulation in any genetic model of a brain disorder (van Dellen et al., 2000). Subsequently, enrichment has been shown to exert a range of molecular, cellular and behavioural effects in HD mouse models (Hockly et al., 2002, Spires et al., 2004a, Spires et al., 2004b, Lazic et al., 2006, Nithianantharajah et al., 2008, Pang et al., 2009; Du et al., 2012).

The first demonstration of environmental enrichment correcting cognitive impairment in a transgenic mouse model of HD indicated that the effects of enrichment are largely hippocampus-mediated. Pre-motor symptomatic R6/1 transgenic mice develop deficits in spatial memory based on their performance on the object location task (but not novel object recognition) and analysis of their spatial mapping strategy on the Barnes maze (Nithianantharajah et al., 2008). These were effectively ameliorated by prior housing in enrichment housing conditions which was concurrent with rescue of a hippocampal deficit of the post-synaptic density protein, PSD-95. Interestingly, taken together with an absence of any obvious modulation of synaptophysin protein levels, it shows that the cognitive benefits of enrichment could be exerted through selective modulation of post-synaptic structures. Future work could be aimed at identifying enrichment effects on the pre-synaptic site, and expanding current investigations to other brain structures such as the broader cortical regions or striatum which are also involved in specific cognitive processes.

In a separate study of the R6/2 transgenic line, it was claimed that environmental enrichment exerted a sex-specific effect by improving cognitive performance of female R6/2 mice as assessed using the Morris water maze (Wood et al., 2010). However, it is necessary to point out that the interpretation of the results in this study is compromised by the use of R6/2 mice which were swimming significantly less capably than the wild-type controls (slower swimming speeds and greater time spent floating in the test sessions). Free-access to running wheels was also provided as part

of the enrichment paradigm without monitoring the distance run by the mice. Therefore, further work will be required to demonstrate any convincing benefits of cognitive stimulation provided through environmental enrichment in this model, and perhaps with a better selection of cognitive behavioural tests with minimal motor requirements to account for the movement deficits in this transgenic line.

These issues were partially addressed by the same group through an inventive 'brain training' approach (Wood et al., 2011). Wood and colleagues trained R6/2 mice using a novel OX task that required the mice to learn a selective sequence of naughts and crosses. R6/2 mice demonstrated learning progress similar to wild-controls as well as normal memory retention, although failing significantly on subsequent reversal learning. However, through exposure to this learning procedure, R6/2 mice showed improved performance on the Lashley III maze which is a slightly less physically challenging spatial memory test compared to the Morris water maze. This study is arguably one of the first to use cognitive stimulation in isolation as a means of enrichment in such a disease model, which is of significant potential since it is extremely challenging and difficult to quantify the extent of cognitive stimulation environmental enrichment actually confers on individual experimental subjects.

Despite the availability of other mouse models of HD, and even a rat model, there have been no other studies of cognitive rescue with enrichment. This could be due to practical constraints of conducting enrichment experiments for extended periods of time with these slower progressing models. However, this would clearly be more relevant and reflective of the human condition and thus warrants future research.

HD animal models provide one of the few examples where the effects enhanced physical activity (e.g. via wheel running) have been directly compared with those of environmental enrichment, outlined above. One interesting aspect of this comparison are the effects on adult neurogenesis in the dentate gyrus of the hippocampus (reviewed by Ransome et al., in press). Adult hippocampal neurogenesis deficits were first demonstrated in the R6/1 and R6/2 mouse models (Lazic et al., 2004, Gil et al., 2005, Grote et al., 2005) and have since been replicated in other models. However, environmental enrichment, which induces a substantial delay in onset of hippocampal-dependent cognitive deficits of R6/1 HD mice (Nithianantharajah et al., 2008), only had subtle effects on adult hippocampal neurogenesis (Lazic et al., 2006). Furthermore, as discussed above, the hippocampal neurogenesis deficits were not rescued by wheel running in the R6/2 (Kohl et al., 2007) or R6/1 (Renoir et al., 2012b) HD mice, despite the fact that running induced hippocampal-dependent cognitive benefits in R6/1 mice (Pang et al., 2006). This implies that environmental enrichment and physical activity may induce their cognitive enhancing effects via actions outside the dentate gyrus, including the effects on synaptogenesis and synaptic plasticity described elsewhere in this review.

3.4. Enrichment improves motor learning in Parkinsonism models

The apparently specific modulation of hippocampal function by environmental enrichment is surprising, but is perhaps the result of a) a limit to the types of cognitive assays for rodent cognition, and b) the nature of the models upon which enrichment has been trialled. For the latter, one could speculate that disorders with pathology that do not largely impact on hippocampal function are unlikely to demonstrate any beneficial cognitive effects of enrichment. Pharmacological lesion models of Parkinsonism fall into such a category due to the methods used to initiate pathology. To mimic the progressive loss of dopamine neurons in the substantia nigra pars compacta (SNpc), MPTP can be administered resulting in cell death in the SNpc. However, housing in enriched conditions is neuroprotective and was shown to prevent cell loss associated with a marked increase in glia-derived neurotrophic factor (GDNF) mRNA levels despite a surprising decrease in BDNF expression (Faherty et al., 2005). Interestingly, the neuroprotective effect of enrichment did not involve modulation of the components of dopaminergic signalling such as the monoamine transporters DAT and VMAT2 which remained significantly down-regulated. Thus, environmental enrichment might be capable of region-specific neuroprotective effects through different neurotrophin-mediated mechanisms, however further research is required to address this question. There is already some indirect evidence of this with enrichment increasing the survival of dopaminergic grafts in rat models of PD (Dobrossy et al., 2000, Dobrossy and Dunnett, 2004) which further supports a neuroprotective function of environmental enrichment.

An alternative approach to modelling Parkinsonism is to deplete dopamine through administration of the neurotoxin 6-hydroxydopamine into the nigrostriatal bundle. One study used this model to demonstrate that housing in environmentally enriching conditions prior to the lesion occurring was sufficient to promote functional recovery of a pre-learnt skilled reaching task (Jadavji et al., 2006). However, it is worth noting that while the availability of running-wheels was not specified in this study, the methodology also involves provision of different food types (of high sugar and energy content) to enriched animals in addition to standard rodent chow. As discussed above, with evidence suggesting that nutritional supplementation influences cognitive performance, caution needs to be taken when interpreting this enrichment benefit on acquired motor tasks. Overall, little is known about the broader effects of environmental enrichment across the different brain regions, and how this might impact on region-specific cognitive outputs. There is great scope for future pursuits into this area.

3.5. Neurodevelopmental disorders

The transgenic Ts65Dn mouse is the most widely accepted model for Down syndrome and has been shown to have deficits in spatial learning, working and long-term memory, reduced attention levels and altered responses to novel environments (Reeves et al., 1995, Coussons-Read and Crnic, 1996, Demas et al., 1998, Escorihuela et al., 1998). Based on pharmacological studies, it appears that this phenotype is largely attributable to over-inhibition of neuronal function which can successfully be addressed by $GABA_A$ antagonists (Fernandez et al., 2007). The dysregulation of GABAergic signalling has been further refined to an imbalance of $GABA_B$ and $GABA_A$ inhibition of hippocampal CA1 pyramidal neurons (Best et al., 2012) and that could contribute to the deficit in hippocampal neurogenesis observed in this mouse line (Chakrabarti et al., 2011). However, much less is known about environmental enrichment and its modulatory effects, if any, on GABAergic signalling in the brain. It is therefore unsurprising that there are a limited number of studies using enrichment as a modulator of cognitive performance in rodent models of Down syndrome. Environmental enrichment reportedly rescues the hippocampal neurogenesis deficit of Ts65Dn mice (Chakrabarti et al., 2011) although the combinatorial approach of including running as part of the enrichment paradigm makes it difficult to dissociate the benefits of social and cognitive stimulation from the physical aspects. Future studies should be undertaken with a refinement of the enrichment approaches as these could potentially provide the preclinical evidence to inform the development of clinical interventions that focus either on cognitive behavioural or physical therapies, or a combination of both. Interestingly, one

report suggests a sex-dependent response to enrichment with female Ts65Dn mice performing better in the Morris water maze but male Ts65Dn showing significantly reduced ability to acquire the task (Martinez-Cue et al., 2002). However, in a follow-up study, by modifying the number of mice group-housed per cage (small 2-3 vs. large 8-10), the same group found that Ts65Dn male mice housed in large groups had elevated levels of corticosterone indicative of higher stress (Martinez-Cue et al., 2005) which could potentially impede the learning process. How the social configuration of housing environment can have such a large influence is still unclear although it could be related to subordination since Ts65Dn mice are less aggressive in the resident intruder test, although they do not have a different behavioural response to predators (Martinez-Cue et al., 2006). Acknowledging the potential confound, Begenisic et al, controlled for the number of male Ts65Dn (2-3) housed under environmentally enriching conditions, compared to six female mice per cage, and reported improved spatial learning in the Morris water maze associated with a robust rescue of hippocampal LTP and normalisation of depolarization-evoked release of GABA from synaptosomes (Begenisic et al., 2011). It remains unclear if housing different numbers of mice together could exert a dose-dependent effect on the extent of the spatial learning rescue, or if physical activity alone could account for this rescue (running wheels were provided as part of enrichment in this study) so there is scope for further investigation in this area. It would be especially informative to establish any dose-dependent effects of social interaction in this model based on evidence that social isolation alone is sufficient to prevent exercise-induced proliferation of hippocampal progenitor cells (Leasure and Decker, 2009).

Rett syndrome (RTT) is an X-linked postnatal neurodevelopmental disorder caused by mutations in the gene encoding methyl-CpG binding protein 2 (MeCP2). It is one of the leading causes of mental retardation in females and is characterised by austistic-like behaviour. Mouse models of RTT display motor deficits and anxiety-related abnormalities that are partially rescued by housing in environmentally enriched home cage conditions (Kondo et al., 2008; Kerr et al., 2010b); however the effects are subject to modification by the background strain of the mouse line. In contrast, the ameliorative effects of environmental enrichment on the locomotor activity and motor coordination deficits is more clear (Kondo et al., 2008, Nag et al., 2009, Lonetti et al., 2010). Therefore, more work will be required to better demonstrate the breadth of cognitive impairment in these transgenic lines prior to further examination of the modulatary effects of environmental enrichment.

3.6. Enrichment is neuroprotective against chronic stress

As discussed above, running protects against stress-induced cognitive impairments by altering hippocampal cytostructure. A similar effect of environmental enrichment has recently been demonstrated which, despite the report lacking hippocampal cell proliferation or neurogenesis data, showed significant effects on CA3 dendritic morphology (Hutchinson et al., 2012). Adult Sprague-Dawley rats subjected to chronic restraint stress for 2-3 weeks were protected against stress-induced memory deficits (measured by radial arm water maze performance) and reductions of hippocampal CA3 apical dendrite length. In comparison, but consistent with the protective effects, enrichment housing for two weeks after exposure to chronic stress prevented any decline in radial arm water maze performance but in a manner that was associated with increased branching and complexity of hippocampal CA3 neurons (Hutchinson et al., 2012). This is a clear demonstration that the benefits of environmental enrichment are influenced by the type of insult which emphasizes the need to broaden current investigations into other brain regions, and to further investigate the timing of enrichment exposure as a potentially important experimental parameter.

3.7. Potential environmental-mediated enhancement of cognition in other models of disease?

The evidence that the environment influences cognitive performance of rodent models of disease is substantial, but is also subject to many issues associated with the study design, method of enrichment or even the models themselves. However, this should not be regarded as a deterrent or serve to dissuade researchers from pursuing this avenue of research further. Many other models of neurological conditions which feature cognitive impairment have yet to be subject to close examination with environmental modifiers. Addiction and withdrawal from substances of abuse is closely associated with disruptions of cognitive processing, yet research to date has been limited to understanding addiction neurobiology while little has been attempted to treat the cognitive deficits that develop. Exposure to these compounds has been demonstrated to impact on dendritic morphology of neurons in the nucleus accumbens and prefrontal cortex (Robinson and Kolb, 1999) and inhibits subsequent environmental enrichment-mediated neuronal plasticity in those brain regions (Kolb et al., 2003). However, the effects on hippocampal neurons is less established and deserves further study, especially in the context of hippocampal-dependent learning and memory processes. The potential for a preventative treatment based on the powerful effect of environmental enrichment has been proposed based on its apparent ability to confer resistance to the addictive properties of psychostimulants (reviewed by Laviola et al., 2008). If this was indeed the case for all, if not just a few, addictive compounds, then the possible development of novel cognition-based preventative therapies is very attractive.

Despite the strong evidence of cognitive impairment in schizotypy and schizophrenia (Cochrane et al., 2012, Kitchen et al., 2012) and the relative success of short-term exercise interventions (Pajonk et al., 2010; Takahashi et al., 2012) and long-term cognitive interventions (Hadas-Lidor et al., 2001) for the rehabilitation of schizophrenic patients, little is known about environmental modification of the development of the cognitive dysfunction. Animal models of schizophrenia are widely available but due to the complexity of schizophrenia, these models reflect aspects of the condition or 'schizotypic endophenotypes' (Jones et al., 2011, Nagai et al., 2011). The pathogenesis of schizophrenia is associated with disruption of cortical maturation, hippocampal function and altered synaptic signalling amongst other abnormalities (Lodge and Grace, 2011), which are well-established to be subject to modification by environmental enrichment in experimental models as described in this article. The effects of environmental enrichment have been investigated in a mouse model of schizophrenia, the PLC-β1 knockout mice (McOmish et al., 2008). Intriguingly, while enrichment rescued sensorimotor deficits, it did not ameliorate the Morris water maze spatial memory deficit; possibly because of the abnormally elevated hippocampal neurogenesis which was later discovered in this mouse model (Manning et al., 2012). Further work needs to be done in other animal models of schizophrenia and associated psychiatric disorders.

3.8. Environmental enrichment, enviromimetics and cognitive enhancement

One implication of the dramatic beneficial effects induced by environmental enrichment in animal models of brain disorders is that this approach could be used to identify potential drug targets.

'Enviromimetics' have been proposed as a potential new class of drugs which will mimic or enhance the beneficial effects of cognitive stimulation and physical activity (Hannan, 2004; McOmish and Hannan, 2007). Existing drugs which are known to enhance BDNF expression (one of the molecular effects of cognitive stimulation and physical activity) include specific histone deacetylase (HDAC) inhibitors and selective serotonin reuptake inhibitors (SSRIs). No doubt future enviromimetic drugs will have molecular targets and modes of action which extend well beyond BDNF. Furthermore, in order to identify such novel enviromimetics it will be important to have cellular assays and animal models that are amenable to high throughput screening approaches. Key consideration will be the nature of the cellular changes assayed, such as synaptogenesis, synaptic plasticity or other forms of cellular plasticity, and whether these translate to cognitive enhancement *in vivo*.

4. Shared and dissociable mechanisms mediating the cognitive enhancing effects of physical activity and environmental enrichment

For humans, it is difficult to dissociate physical activity from cognitive stimulation and other environmental factors. Most forms of physical activity can lead to altered sensory and cognitive stimulation as well as social interaction, and *vice versa*, making it challenging to parse the key components. Therefore it is essential that these questions be pursued in animal models, where genetic and environmental factors can be carefully controlled, and levels of physical activity can be increased independent of other variables such as the sensory environment and opportunities for cognitive stimulation.

The extensive body of data reviewed above demonstrates that enhanced physical activity (e.g. running) and environmental enrichment can exert beneficial effects, including cognitive enhancement, in a wide range of animal models of brain disorders. It is of great interest to know to what extent the benefits of environmental enrichment arise from enhanced cognitive activity versus physical activity, as this experimental paradigm can induce both forms of activity. Environmental interventions which provide only running wheels allow physical exercise (albeit in a somewhat stereotyped form) to be examined in isolation. The relative effects of environmental enrichment and physical activity on models of various brain disorders, including those not involving cognitive deficits, have been reviewed (Nithianantharajah and Hannan, 2006). One conclusion which can be drawn is that increased physical activity alone may have exert beneficial effects through initial changes in the periphery, such as increased blood flow and modulation of endocrine and metabolic factors, which in turn impact on brain structure and function. Conversely, the effects of environmental enrichment which do not require increased physical activity, such as enhanced sensory and cognitive stimulation, may have specific effects such as synaptogenesis, synaptic plasticity and other forms of cellular plasticity in discrete brain areas. For example, in wild-type rodents there is evidence that wheel running alone increased levels of cell proliferation in the dentate gyrus, however the enhanced cognitive stimulation, learning and memory associated with environmental enrichment is needed to facilitate enhanced survival of adult-born neurons (van Praag, 2008).

Further investigations using valid animal models are required which systematically compare the effects of environmental enrichment, physical activity and other specific environmental manipulations. Together with retrospective and prospective epidemiology, this may guide the development of future preventative strategies, therapeutic interventions and clinical trials.

5. Conclusion

The disease modifying effects of environmental enrichment and enhanced physical activity have been demonstrated in a variety of rodent models of disease. While the underlying mechanisms of each have yet to be fully elucidated, there is overwhelming evidence that cognitive impairment as part of the various disease processes can be rescued, delayed or even prevented. Enhanced physical activity and cognitive stimulation have shown beneficial effects in many preclinical and clinical studies. Future studies should guide the optimisation of exercise and cognition-based therapeutic programs. Furthermore, identification of molecular mechanisms may facilitate the future development of 'enviromimetic' drugs which could act synergistically with such environmental interventions to mediate maximum benefits in delaying, slowing and eventually curing a range of devastating brain disorders.

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