Caloric restriction, physical activity, and cognitive performance: A review of evidence and a discussion of the potential mediators of BDNF and TrkB

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Abstract:

Lifestyle behaviours, such as eating and physical activity (PA), have been recognised as factors that may influence age-related cognitive decline. A high-fat diet and sedentary behaviour have been associated with poor cognitive performance in a variety of domains, in both animals and humans, while caloric restriction (CR) and PA are typically associated with positive outcomes. The lifestyle-associated changes in cognitive performance typically involve areas of the brain that are vulnerable to structural alterations, such as the hippocampus. Here, we frame age-related cognitive change in regard to the brain and cognitive reserve theories and discuss the potential for CR and PA interventions, independently and in combination, to affect cognitive trajectories. We provide mechanistic support for these interventions to affect cognitive performance through BDNF and its high-affinity receptor TrkB. Further, we offer suggestions for future study designs to investigate these relationships and urge researchers to be mindful of the potential mediating roles of BDNF and TrkB.

Keywords: high-fat diet | ageing | hippocampus | age-related cognitive decline

Article:

Given the increase in the population of older adults and the expectation that the number of older American adults will more than double from the years 2010 to 2050, age-related changes in functioning are important targets for research efforts. One type of functioning that is particularly relevant to older adults is cognitive functioning. For many people, cognitive deficits are a facet of the ageing process, and much effort has gone into uncovering interventions that may delay age-related cognitive decline. Although age is a primary risk factor for cognitive impairment, additional modifiable risk factors, such as consumption of a high-fat diet and physical inactivity, are known to contribute to a person's risk of cognitive decline. This is particularly problematic given that these two lifestyle behaviours are essentially normative in Western societies. The

purpose of this review is to consider the evidence with regard to a particular dietary modification (caloric restriction [CR]) and physical activity (PA) to better understand how these behaviours may influence neural pathways, which may then improve or maintain cognitive performance. Although lifestyle behaviours have important health benefits for people of all ages, the cognitive reserve theory suggests that these behaviours will benefit cognition primarily for those who are experiencing decrements due to factors like ageing, clinical cognitive impairment, or traumatic brain injury. Thus, we begin with a brief description of the cognitive reserve theory as a framework from which to understand how diet and PA influence cognition particularly for those with challenges to their cognitive reserves.

Cognitive reserve theory

Stern (2012) suggested that age-related cognitive decline is largely determined by brain structure (brain reserve) and brain function (cognitive reserve) and that these reserves are influenced by variables such as age, education, occupation, and leisure activity. Enhanced cerebral structure is thought to provide the necessary brain reserves to compensate for pathological changes and delay the onset of symptoms of cognitive decline with advancing age (Katzman et al., 1988). Similarly, having an increased cognitive reserve may influence the resilience of neural networks against pathological change and allow for efficient cognitive processing through primary or compensatory pathways.

The hippocampus is important for cognitive performance and has been shown to change with advancing age in a manner consistent with the postulates of cognitive reserve theory. The structure of the hippocampus has been shown to have an annual atrophy rate of 1–2% in people age 55 and older without dementia (Erickson et al., 2010; Jack et al., 1998). Additionally, studies have shown the link between brain and cognitive reserves by identifying functional impairments in hippocampal-dependent processes, such as learning and memory, following hippocampal atrophy or structural damage (Broadbent, Squire, & Clark, 2004; Erickson et al., 2010). Lastly, hippocampal-based cognition relies on efficient, organised, spatial patterns of neural networks, which then provide hippocampal-specific cognitive reserve (Stern et al., 2008; Stern, 2012). These cognitive neural networks contain many individual neurons that form synapses on their dendritic spines to communicate with other neurons. The neural dendritic spine is responsible for about 90% of excitatory synapses in the brain (Bonhoeffer & Yuste, 2002) and synaptic plasticity (i.e. efficacy of the synapse) has been noted as an important regulatory component of hippocampal-related cognition (Bourne & Harris, 2008; Karimi et al., 2013). Regulation of synaptic plasticity is controlled by the opposing processes of long-term potentiation (LTP) and long-term depression (LTD). LTP promotes synaptic strength through growth of the dendritic spine and increased post-synaptic receptors (Citri & Malenka, 2008; Minichiello, 2009). In contrast, LTD reduces the size of dendritic spines and the density of receptors (Citri & Malenka, 2008). Ideally, there would be a tightly regulated balance of LTP and LTD to optimally strengthen and prune the dendritic spine, but with advancing age, LTD becomes dominant resulting in an overall imbalance with greater amounts of neural degeneration (Minichiello, 2009).

Though changes in hippocampal structure and function have been shown to be part of normal ageing, lifestyle factors seem to play a key role in this neurodegenerative process as well.

Transitioning from being active to sedentary at a young age is associated with decreased hippocampal neurogenesis in mice (Nishijima et al., 2013), and subsequent research has shown that hippocampal neurogenesis is associated with reduced hippocampal grey matter (Biedermann et al., 2012). Additionally, in their review of the extant literature, Kanoski and Davidson (2011) implicated the western diet (high saturated fat and simple sugar intake) as a major contributor to hippocampal atrophy and associated cognitive deficits in humans and animals. Similarly, synaptic plasticity can be affected by lifestyle factors such as consuming a high-fat diet for six months, which has been associated with a blunted LTP response in rats (Karimi et al., 2013).

The converse is also true in that lifestyle behaviours have been shown to have a positive effect on hippocampal structure and function. Studies with both humans and animals have shown that maintaining a normal weight and being physically active are associated with benefits to hippocampal structure (Biedermann et al., 2012; Erickson et al., 2011; Kanoski & Davidson, 2011; Raji et al., 2010; Varma et al., 2014) and increased synaptogenesis (Creer, Romberg, Saksida, van Praag, & Bussey, 2010; van Praag, Kempermann, & Gage, 1999). These benefits are also associated with improved cognitive performance (Erickson et al., 2011).

Given the evidence supporting that cognitive reserves are influenced by age and lifestyle factors and our interest in understanding how the behaviours of PA and diet can ultimately influence cognition, we turn now to an explanation of putative mechanisms linking these behaviours to cognition. Specifically, we focus on potential mediating factors of BDNF and the associated TrkB signalling cascade to further understand these relationships. Before describing the research in this area, it is important to provide an overview of how BDNF affects hippocampal structure and function and to explain the TrkB signalling cascade so that specific effects on aspects of this system can be explained. Descriptions of all abbreviations associated with BDNF and TrkB are provided in Table 1.

Table 1. Abbreviations.

Abbreviation	Full name
BDNF	Brain-derived neurotrophic factor
tPA	Tissue plasminogen activator
TrkB	Tyrosine Kinase B
$p75^{NTR}$	p75 neurotrophin receptor
Shc	Src homology 2 domain containing adaptor protein
PLCγ1	Phospholipase C, gamma 1
Ras	Ras guanosine-nucleotide-binding protein
MEK	Mitogen/extracellular signal-regulated kinase
MAPK[a]	Mitogen-activated protein kinase
ERK[a]	Extracellular-regulated kinase
PI3K	Phosphoinositide 3-kinase
Akt	Serine-threonine kinase
BAD	Bcl-2-associated death promoter
CREB	Cyclic adenosine monophosphate response element-binding protein
IP_3	Inositol triphosphate
DAG	Diacylglycerol
CAMKs	Calmodulin-dependent protein kinases
PKC	Protein kinase C
Ca^{++}	Calcium

[a]MAPK was originally termed ERK and is noted as MAPK/ERK throughout this review.

Brain-derived neurotrophic factor

Synaptic plasticity along with neuronal development and survival rely heavily on neurotrophin expression in the brain (Reichardt, 2006). Specifically, the expression of BDNF is a mechanism that is thought to underlie local improvements in synaptic plasticity and cognitive performance (Erickson et al., 2010). An age-related decline in BDNF has been recognised in animals and humans (Erickson et al., 2010; Silhol, Bonnichon, Rage, & Tapia-Arancibia, 2005) and postulated as an important mediator of the age-related changes in hippocampal volume and memory (Erickson et al., 2010). Importantly, both PA and a high-fat diet have been shown to influence BDNF. In young and aged rats, high-fat diets have been shown to result in reductions in BDNF expression and detriments to performance on spatial learning and memory tasks (Kishi et al., 2015; Molteni et al., 2004; Stranahan et al., 2009; Woo, Shin, Park, Jang, & Kang, 2013; Wu, Ying, & Gomez-Pinilla, 2004). In contrast, CR and/or PA have been shown to increase the expression of BDNF and to upregulate the TrkB signalling cascade (Kishi et al., 2015; Smiljanic et al., 2014; Stranahan et al., 2009). Therefore, CR and PA may serve as potential interventions to upregulate BDNF, increase hippocampal plasticity, and prevent or reverse lifestyle- or age-related cognitive decline.

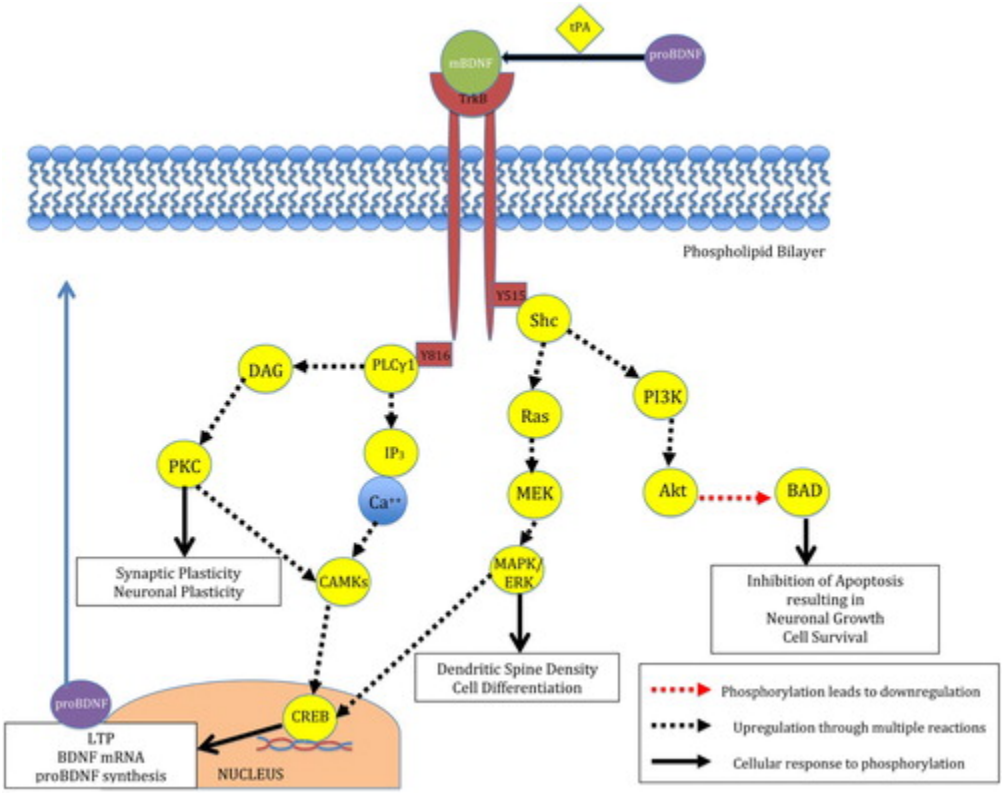

Figure 1. Illustration of the TrkB pathway.

BDNF is concentrated in the hippocampus and is expressed in two isoforms, the precursor (proBDNF) and mature (mBDNF) forms. ProBDNF is limited to binding to $p75^{NTR}$ and is associated with neuronal cell death and LTD (Reichardt, 2006). Though mBDNF can bind with $p75^{NTR}$, it predominately binds to its high-affinity receptor TrkB, which stimulates a signalling

cascade ultimately leading to increases in dendritic spine density, LTP, neuronal survival, and transcription of BDNF mRNA (Alonso, Medina, & Pozzo-Miller, 2004; Longo & Mattson, 2014; Minichiello et al., 2002; O'Callaghan, Ohle, & Kelly, 2007; Tao, Finkbeiner, Arnold, Shaywitz, & Greenberg, 1998). For the purpose of this review, the sequence of molecular interactions moving from mBDNF to BDNF mRNA transcription will be referred to as the TrkB signalling cascade (illustrated in Figure 1).

TrkB signalling cascade

As previously described, proBDNF is not able to bind to the TrkB receptor but rather must first be converted to mBDNF by tPA to exert any influence on the TrkB signalling cascade. Thus, when examining the TrkB signalling cascade, it is important to note that BDNF activation of TrkB is originating from mBDNF. TrkB has two major docking sites, Shc and PLCγ1 (Minichiello et al., 2002). Through the TrkB–Shc docking site, two intracellular pathways are activated. Ras, a guanosine triphosphatase, activates MEK, which further phosphorylates and activates MAPK/ERK. Increased activation of the Ras/MAPK pathway is associated with increased dendritic spine density and cell differentiation (Alonso et al., 2004; Bucci, Alifano, & Cogli, 2014). TrkB–Shc also gives rise to the PI3K/Akt pathway. Most notably, the PI3K/Akt pathway has been shown to phosphorylate and inactivate BAD. Since BAD is responsible for apoptosis (cell death), this inactivation of BAD results in the inhibition of apoptosis, which then indirectly promotes neuronal growth and survival (Brunet, Datta, & Greenberg, 2001; Bucci et al., 2014).

The functional changes resulting from BDNF and TrkB have been extensively reviewed (Minichiello, 2009), thus we focus on the general mechanisms proposed to affect cognition. As previously explained, synaptic plasticity, regulated by LTP and LTD, has been noted as one of the most important factors for influencing learning and memory (Bourne & Harris, 2008; Karimi et al., 2013). To explain LTP further, it consists of three major components: induction, maintenance, and expression (Sweatt, 1999). Gene transcription and protein synthesis are required for LTP expression, which is necessary for long-term cognitive effects; this is otherwise noted as synaptic consolidation (Gruart, Sciarretta, Valenzuela-Harrington, Delgado-Garcia, & Minichiello, 2007; Minichiello, 2009; Morris et al., 2003). Downstream of the TrkB signalling cascade, CREB signalling has consistently been described as one of the key regulators of synaptic consolidation through its influence on LTP (Hu, Long, Pigino, Brady, & Lazarov, 2013; Tao et al., 1998). Though controversial (see Minichiello et al. (2002) and Gruart et al. (2007) for evidence to the contrary), the TrkB–Shc activation of the Ras/MAPK pathway has been shown to influence LTP, in a CREB-dependent manner (Alonso et al., 2004; Reichardt, 2006; Ying et al., 2002). More consistently, the PLCγ1 docking site on TrkB and the subsequent signalling cascade has been shown to regulate LTP through a Ca^{++}-dependent pathway (Bucci et al., 2014; Gruart et al., 2007; Minichiello et al., 2002) and is necessary for synaptic consolidation (Gruart et al., 2007). To further explain this pathway from the PLCγ1 docking site, activation of IP_3 or DAG leads to protein signalling. Upon IP_3 activation, Ca^{++} is released from intracellular stores, which activates CAMKs leading to the phosphorylation of CREB. In turn, these reactions increase transcription of BDNF mRNA, proBDNF protein synthesis, and LTP (Bucci et al., 2014; Minichiello et al., 2002; Reichardt, 2006; Tao et al., 1998). TrkB–PLCγ1 can additionally activate DAG, which increases the expression of PKC signalling and leads to

synaptic and neuronal plasticity (Bucci et al., 2014; Reichardt, 2006). Though the Ras/MAPK pathway can lead to CREB signalling and transcription, the Ca^{++}-dependent pathways originating at TrkB–PLCγ1 are recognised as being responsible for about 80% of BDNF transcription (Tao et al., 1998), which is required for LTP (Gruart et al., 2007; Minichiello, 2009; Morris et al., 2003).

Given the link between BDNF, BDNF mRNA transcription, and LTP the identification of interventions that can influence BDNF expression and the TrkB signalling cascade may provide promise for making an impact on hippocampal-related cognitive outcomes. We turn next to an examination of the extant literature relative to the effects of CR and PA on this signalling cascade and cognitive performance outcomes (see Table 2).

Caloric restriction

CR by way of daily energy restriction or intermittent fasting is one possible intervention that may influence various aspects of the TrkB signalling cascade in a fashion that may ultimately affect cognitive performance. Daily energy restriction in this area of research is typically defined as a 20–40% reduction in caloric intake, without malnutrition (Goldberg et al., 2015). Intermittent fasting refers to abstaining from energy intake for 16–24 hours and has similar general health benefits as compared to daily energy restriction (van Praag, Fleshner, Schwartz, & Mattson, 2014). CR has positive effects related to longevity – it is the only intervention shown to increase lifespan in short-lived species such as flies, fish, mice, and rats with increases in lifespan of up to 60% (Hosono, Nishimoto, & Kuno, 1989; Redman, Martin, Williamson, & Ravussin, 2008; Taormina & Mirisola, 2014) and it can prevent cardiovascular disease, diabetes mellitus type 2, and obesity in long-lived species (Fontana et al., 2007; Lefevre et al., 2008). It has also been noted that CR can delay age-related declines in learning, spatial and working memory, and neurotrophic factor expression in the hippocampus with evidence that this occurs through the TrkB signalling cascade (Komatsu et al., 2008; Murphy, Dias, & Thuret, 2014; Pitsikas & Algeri, 1992).

In particular, CR can positively influence expression of hippocampal BDNF (Duan, Lee, Guo, & Mattson, 2001; Kishi et al., 2015; Stranahan et al., 2009), phosphorylation of CREB (Fusco et al., 2012), dendritic spine density (Stranahan et al., 2009), and transcription of BDNF (Duan et al., 2001; Smiljanic et al., 2014). Seminal work in this area by Duan et al. (2001) provided novel evidence for an increase in BDNF expression and transcription through intermittent fasting. Greater expression of hippocampal BDNF and increases in dendritic spine density were also found after three months of 40% CR (Stranahan et al., 2009). Though not assessed in these particular studies, previous mechanistic work supports increased BDNF and dendritic spine density leading to improved performance on hippocampal-related cognitive tasks such as learning and memory (Alonso et al., 2004; Kishi et al., 2015; Minichiello, 2009).

Table 2. Details and findings for studies exploring the effects of CR, PA, or a combination of CR and PA.

		Subjects									Findings	
	Reference	**A/H**	**Characteristics**	***n***	**Mean age**	**Sex**	**Experimental conditions**	**Length of Tx**	**Cognitive task**	**Cognitive domain**	**Effect on pathway components**	**Cognitive performance**
CR	Duan et al. (2001)	A	Sprague-Dawley	120	3 months	M	CR: EODF Control: AL	3 months	N/A	N/A	Increase BDNF protein and BDNF mRNA in hippocampus and cortex	N/A
	Witte et al. (2009)	H	Normal-OW	50	60.5 years	M/F	CR: 30% reduction Increase 20% UFA Control	3 months	Rey Auditory Verbal Learning Task	Memory	No change in serum BDNF	Memory score improved only in CR group
	Fusco et al. (2012)	A	BCKO and control mice	NR	5 months	M	CR: BCKO: 40% reduction CR: Control strain: 40% reduction AL-BCKO AL-Control strain	5 weeks	Novel object recognition	Object memory	Increased hippocampal LTP, CREB phosphorylation in CR-control only	Improved memory peformance in CR-control, but not CR-BCKO
	Yang et al. (2014)	A	C57 mice	75	3 months	M	CR: 30% reduction Control: AL	9 or 17 months	Morris Water Maze	Spatial learning and memory	Decreased BDNF, PI3K, Akt expression and phosphorylation of Akt in the hippocampus	Improved MWM performance to age-matched AL controls at 12 and 20 months
	Smiljanic et al. (2014)	A	Wistar rats	25	3 months	M	CR: EODF Control: AL	9 or 21 months	N/A	N/A	Increased BDNF mRNA at 12, but not 24 m. Increase proBDNF in hippocampus and cortex with CR at 24. Increased mBDNF in cortex at 12 m, but decreased at 24 m in cortex and hippocampus	N/A
	Kishi et al. (2015)	A	Sprague-Dawley high-fat diet induced metabolic syndrome rats	25	13 weeks	M	CR + vehicle: 30% reduction CR + A: 30% reduction with TrkB anatagonist High-fat diet (32% fat)	28 days	Morris water maze	Spatial learning and memory	BDNF increased in CR and CR + A, but significantly decreased with high-fat diet	Improved MWM performance with CR compared to high-fat diet. Benefits attenuated with TrkB antagonist

		Subjects									Findings	
	Reference	**A/H**	**Characteristics**	***n***	**Mean age**	**Sex**	**Experimental conditions**	**Length of Tx**	**Cognitive task**	**Cognitive domain**	**Effect on pathway components**	**Cognitive performance**
	Scott et al. (2014)	H	Normal-OW	218	Adult	M/F	CR: 25% AL-control	24 months	Cognitive battery	Reaction time, attention/vigilance, verbal and visual memory, working memory, executive function	N/A	No significant differences
PA	Vaynman et al. (2004)	A	Sprague-Dawley	28	3 months	M	PA: VWR with TrkB inhibitor PA:VWR with cytC Sedentary with cytC Sedentary with TrkB inhibitor	3 or 7 days	N/A	N/A	Increased BDNF and synapsin I with exercise, when blocking TrkB receptor, BDNF increased with reduced levels of synapsin I	N/A
	Zoladz et al. (2008)	H	Healthy, active	13	22.7 years	M	PA: 40 min continuous cycling (2 days/week) PA: ~40 min intermittent cycling (2 days/week)	5 weeks	N/A	N/A	Resting BDNF levels and change in BDNF pre-post levels significantly increased after training	N/A
	Aguiar et al. (2011)	A	Wistar rats	35	24 months	F	PA: Short bouts of mild-intensity TM exercise (4 days/week) Sedentary control	5 weeks	Morris water maze Open field task Step-down task	Spatial learning and memory Locomotor activity Short- and long-term memory	Increased phosphorylation of Akt and CREB, BDNF mRNA expression, and BDNF protein levels in the hippocampus.	Improved spatial learning and memory
	Ding et al. (2011)	A	Sprague-Dawley	28	Adult	M	PA:VWR Sedentary	7 days	N/A	N/A	Exercise increased proBDNF (148%) and mBDNF (211%). Positive corrrelation with mBDNF and running distance. Exercise increased pTrkB, pERK, pAkt, and pCaMKII. This	N/A

		Subjects									Findings	
	Reference	A/H	Characteristics	*n*	Mean age	Sex	Experimental conditions	Length of Tx	Cognitive task	Cognitive domain	Effect on pathway components	Cognitive performance
											finding was disrupted with blocking tPA-proBDNF (107%), mBDNF (96%). Blocking tPA increased proBDNF to 158% and decreased mBDNF to 79%.	
	Erickson et al. (2011)	H	Sedentary	120	66.5 years	M/F	PA: 40 min progressive walking programme Stretching/Toning control	12 months	Spatial memory task	Spatial memory	Increased hippocampal volume by 2%, associated with higher BDNF	Hippocampal volume related to memory performance
	Chapman et al. (2013)	H	Sedentary	37	64 years	M/F	PA: 60 min TM or cycling 50–75% MHR Wait list control	12 weeks	TrailsB/TrailsA CVLT-II WMS-IV	Executive function Memory Immediate/delayed memory	N/A	Improved immediate/delayed memory.
									DKEFS Backward digit span	Complex attention Complex attention		
CR plus PA	Stranahan et al. (2009)	A	dBdB and WT	48	1 month	M	CR: 40% restriction PA: VWR CR + PA: – 40% + VWR	3 months	N/A	N/A	Increased DSD and HC BDNF with CR, PA, and CR + PA in dBdB mice. Increased DSD and HC BDNF with CR or PA with additive benefits of CR+PA in WT mice.	N/A
	Khabour et al. (2010)	A	Wistar rats	NR	5 months	M	CR: EODF CR + PA: EODF + VWR Control	1.5 months	Radial Arm Water Maze	Spatial learning and memory	Increase in BDNF only with combined intervention	Increase learning performance and memory formation only with CR + PA
		H	Sedentary	107	70 years	M/F	CR: 500–750 cal/day reduction PA: 3	12 months	3MS	General cognitive function	N/A	Increase in 3MS in all conditions, but

		Subjects									Findings	
	Reference	**A/H**	**Characteristics**	***n***	**Mean age**	**Sex**	**Experimental conditions**	**Length of Tx**	**Cognitive task**	**Cognitive domain**	**Effect on pathway components**	**Cognitive performance**
	Napoli et al. (2014)						days/week, 90 min/day/65% HRmax + RT CR + PA: combined interventions		Word Fluency	Verbal production, semantic memory, language		significantly higher in CR + PA. Improved word fluency in PA and CR + PA. Improved trail making with CR + PA only.
									Trail Making	Executive function		

A: animal; A/H: animal or human subjects; AL: *ad libitum*; BCKO: brain CREB knockout mice; cytC: cytochrome C (control strain); dBdB: leptin deficient mice strain (metabolic syndrome model); DSD: dendritic spine density; EODF: every other day feeding; F: female; H: human; M: male; M/F: male or female subjects; MHR: max heart rate; NR: not reported; N/A: not assessed; OW: overweight; TM: treadmill; VWR: voluntary wheel running; WT: wild type.

Recently, studies have assessed both mechanistic changes and cognitive outcomes in response to CR. Kishi et al. (2015) found that a 30% CR intervention increased BDNF, decreased oxidative stress, and improved memory and learning performance in rats with metabolic syndrome. Interestingly, when they introduced a TrkB antagonist the cognitive performance outcomes were diminished. This suggests that memory and learning performance are dependent on TrkB signalling. Fusco et al. (2012) examined the effects of 40% CR in normal and CREB knockout mice. Their study allowed for a determination of the specific role of CREB as a potential mediator, within the TrkB signalling cascade, of the CR and cognitive performance relationship. They found that CREB knockout mice performed significantly worse than controls on cognitive tasks regardless of diet. However, the normal mice that were restricted in diet performed better in the cognitive tasks than all other groups and had increased LTP. These findings suggest that CR has a positive influence on synaptic consolidation in a TrkB signalling- and CREB-dependent manner.

In contrast, some studies show that after significant periods of CR (9–17 months) or intermittent fasting (12–24 months), no effect or a negative effect on hippocampal BDNF expression is observed (Smiljanic et al., 2014; Yang et al., 2014). Despite a decrease in BDNF expression and PI3K/Akt activation, better cognitive outcomes compared to age-matched controls have still been reported with CR (Yang et al., 2014). The authors of these studies suggest that mechanisms controlling autophagy, a process that rids dysfunctional proteins from cells thought to accumulate with age and unhealthy lifestyle (Cui, Yu, Wang, Gao, & Li, 2013; Yang et al., 2014), is the underlying reason for the observed improvement in cognition from CR interventions. However, the larger body of evidence has been consistent in associating CR with better cognitive performance with evidence that this occurs through an upregulation of the TrkB signalling cascade.

Though evidence from animal models seems promising in suggesting that CR leads to improved cognitive performance and that these improvements are mediated by BDNF and/or the TrkB pathway, studies on humans are much more limited. In humans, the blocking of receptors and pathways to test mechanisms is, of course, not possible nor are we able to assess BDNF in the CNS which limits the ability to directly and causally test the role of putative mechanisms. For this reason, the focus in these studies has been on cognitive outcomes. Further, there are only three published studies on this topic and the results of these studies are mixed. Witte, Fobker, Gellner, Knecht, and Flöel (2009) found improved memory performance, despite no change in peripheral BDNF, after three months of 30% CR. In contrast, Scott et al. (2014) reported no changes in cognitive performance with 25% CR. In these two studies, CR was prescribed as a per cent reduction in caloric intake, so it is difficult to compare the findings with the third study in which CR was prescribed as an absolute amount designed to result in weight loss equivalent to 10% of body weight. In this study, the authors reported a significant improvement in obese older adults' cognitive performance after one year of restricting daily energy intake by 500–750 calories (Napoli et al., 2014).

This last study brings up an important point which is that studies exploring the effects of CR on cognition must also consider the implications of weight loss. As expected with CR, a decrease in body weight is typically found (Lefevre et al., 2008; Ma et al., 2015; Napoli et al., 2014; Smiljanic et al., 2014; Witte et al., 2009). Though this may be a positive outcome for those who

are overweight or obese, it may not be appropriate for normal-weight individuals. Potential downsides of CR, reviewed extensively elsewhere (Dirks & Leeuwenburgh, 2006), are loss of muscle mass, decrease in bone mineral density, hormone changes, and hypotension. These negative effects cannot be ignored because lesser muscular strength is predictive of disability and all-cause mortality (Rantanen et al., 1999) and decreased bone mineral density can lead to frailty and fractures that affect quality of life (Villareal et al., 2011). Therefore, CR as an independent intervention for cognitive decline may not be appropriate for everyone.

Physical activity

Regular PA has also been shown to reduce the risk for many diseases and disorders including, but not limited to, cardiovascular disease, diabetes mellitus type 2, obesity, cancer, and age-related cognitive decline (Hardman, 2001; van Praag et al., 2014; Varma, Chuang, Harris, Tan, & Carlson, 2015). PA can improve cognitive function through promoting neuroplasticity, cerebral blood flow, angiogenesis, and expression of neurotrophins (Carvalho, Rea, Parimon, & Cusack, 2014). Specifically, in response to aerobic exercise, circulating BDNF has been shown to increase in humans (Erickson et al., 2011; Zoladz et al., 2008) and hippocampal BDNF has been shown to increase during and after exercise in animals (Chapman et al., 2012; Khabour, Alzoubi, Alomari, & Alzubi, 2010; Vaynman, Ying, & Gomez-Pinilla, 2004).

In addition to evidence that PA is associated with an increase in hippocampal BDNF (Khabour et al., 2010), research has similarly demonstrated improvements in cell signalling, tissue plasminogen activator (tPA) expression, and TrkB expression. Ding, Ying, and Gomez-Pinilla (2011) postulated that PA increases tPA, a facilitating factor in the conversion of proBDNF to mBDNF, and in turn contributes to the regulation of the TrkB signalling cascade. mBDNF has a higher affinity for the TrkB receptor than does proBDNF and therefore catalysing this conversion may increase TrkB binding and stimulate the signalling cascade (Ding et al., 2011). Given exercise may increase mBDNF in the hippocampus and upregulate the TrkB signalling cascade, these effects may explain exercise-related improvements in cognition. Aguiar et al. (2011) found that short bouts of mild-intensity exercise, four times per week, for one month lead to significant increases in BDNF protein levels, BDNF mRNA expression, Akt, and CREB signalling in aged rats. This upregulation of the TrkB signalling cascade was also accompanied by better learning and memory performance.

Though a large proportion of the exercise and BDNF research has been conducted with rodents, moderate intensity exercise has been shown to increase circulating BDNF in humans with associated improvements in hippocampal volume and spatial memory performance (Erickson et al., 2011; Zoladz et al., 2008). Thus, there is support for the role of BDNF and the TrkB signalling cascade as mechanisms underlying the effects of exercise on cognition that have been observed in both human and animal studies.

CR and PA

Given that CR and PA have been shown to independently influence the TrkB signalling cascade and to have resultant beneficial effects on cognitive performance and given that CR in isolation has negative health effects that might be minimised by increasing PA, an important direction for

research is to consider the potential combined effects of these two behaviours. Thus far, this has only been examined in a small number of studies focused on overall negative energy balance. This negative energy balance is achieved either with a prescribed reduction in energy intake from CR and a prescribed increase in energy output from PA (Huffman et al., 2008; Lefevre et al., 2008) or a prescribed energy reduction through CR with voluntary exercise with self-determined energy requirements (Khabour et al., 2010; Stranahan et al., 2009). Though evidence is limited, positive outcomes have been reported in both animals and humans when combining these behaviours.

Stranahan et al. (2009) examined the effects of 40% CR, voluntary wheel running (VWR), and a combination of both for 12 weeks on neuroplasticity and diabetic markers in young insulin-resistant and wild-type mice. They found that in all treatment conditions serum insulin decreased and BDNF increased with an associated increase in dendritic spine density. Interestingly, when combining CR with VWR additive effects of BDNF were noted in the wild-type mice, which the authors suggested was due to increased energy metabolism in the periphery. Khabour et al. (2010) assessed the effects of CR (every other day fasting) by itself and of CR combined with VWR for 6 weeks in young rats. They found that with CR alone there were no changes to BDNF or cognitive performance. However, when combined with VWR, a significant increase in BDNF along with improvements in learning and memory function were noted. Similar to previous findings, they reported a two- to fourfold increase in VWR during the calorically restricted periods. The latter finding is often referred to as a food-restriction-induced hyperactivity in animals (Khabour et al., 2010) and would not be expected in human interventions. However, human studies with older adults do find similar benefits to cognition when CR and PA are combined.

Napoli et al. (2014) found that obese older adults can cognitively benefit from an intervention of CR and PA. After 12 months of the intervention, general cognitive performance measured by the modified mini-mental state (3MS) test was best in the group combining a prescribed aerobic and resistance training programme with a restriction in calories (about 500–750 per day) as compared to CR or PA alone. Additionally, when combining CR and PA, benefits to executive function were significant, whereas no improvements were found for CR or PA alone. Executive function, similar to hippocampal-related cognition, is vulnerable to senescence (Buckner, 2004). Though hippocampal-related cognition was not an outcome measure of this study, the results suggest that a combined intervention programme is superior to that of CR or PA alone for cognitive performance in this population.

Other studies that have examined this type of effect in younger populations, who are not necessarily at risk for cognitive decline, did not find similar results. The CALERIE study was the first major human study examining the effects of a 25% decrease in energy, through CR or CR and PA, on general health biomarkers and cognitive performance in 20–50 years old, healthy, non-obese participants (Lefevre et al., 2008; Scott et al., 2014). After 6 months, significant improvements in cardiovascular disease risk factors such as lipid profiles and blood pressure were found. However, at 6, 12, and 24 months of follow-up no main effect for changes in cognitive performance was found (Scott et al., 2014). Although this finding was not what the authors hypothesised, it is not surprising given their sample population. The subjects were young and healthy and were not experiencing cognitive impairments that would have been expected to

respond to a behavioural intervention. However, although the findings do not show benefits for cognition, they do suggest that CR and PA can be beneficial to physical health in a young to middle-aged healthy population without negatively affecting cognition. Future studies should focus on older adults or on other populations expected to be experiencing cognitive decrements to examine the effects of this type of intervention on cognition.

Findings from animal studies provide evidence that a combined intervention of CR and PA affects brain structure and function, through increases in BDNF, and there is some limited evidence for cognitive benefits. With humans, the extant literature only supports benefits for older adults who have presumably experienced age-related cognitive decline. BDNF and the TrkB signalling cascade appear to mediate interventions that alter energy balance (CR, PA, CR, and PA) and cognitive performance. Though there is promising evidence for this relationship in animals, through mechanistic support, the studies on humans is less clear and further research is needed.

Conclusion

The evidence reviewed herein provides clear support for the positive effects of CR and PA on cognition and provides some evidence in support of the roles of BDNF and the TrkB signalling cascade in explaining these effects. An interesting question that has only begun to be explored is whether or not these interventions can be combined in a way that would result in maximal benefits to cognition. Given that CR and PA, independently, increase specific parts of the TrkB signalling cascade, impact neural and synaptic plasticity, and have positive hippocampal-related cognitive outcomes, this is an important direction for future research. Even if the combination of the interventions does not have additive benefits for cognition, this type of intervention may be well-suited for human application. As described, CR interventions have shown a dose–response effect on animal lifespan and cognitive performance (Weindruch, 1996), but CR interventions might not be applicable to the human model because of the associated negative health implications of CR in isolation. A combination of CR and PA may help achieve a similar negative energy balance, but minimise the risk of muscle loss, low bone mineral density, hormone changes, and hypotension, associated with chronic CR in humans (Mercken, Carboneau, Krzysik-Walker, & De Cabo, 2011).

As discussed in this review, the TrkB signalling cascade is important for hippocampal-related cognitive performance. Both CR and PA have been shown to affect cognitive performance independently and synergistically with some evidence that the TrkB signalling cascade is involved. However, CR and PA also affect oxidative stress, which has been associated with changes in the TrkB signalling cascade and hippocampal-related cognition. This is a relationship that is being explored relative to the effects of CR and PA on cognition and is deserving of further attention. An additional consideration relative to this review is that although the cognitive reserve theory focuses on benefits of lifestyle behaviours for those with cognitive challenges, the animal literature exploring the benefits of CR, PA, and the combined effects of CR and PA has predominantly consisted of studies on young animals that would not be expected to realise the same benefits as might older or cognitively impaired animals. The evidence with humans shows more of a mix with regard to the age of the samples, but importantly the most promising evidence for benefits of CR, PA, and CR and PA in combination for cognitive performance are

observed in studies with older adults. Hence, it will be important for future studies to focus on older populations to best advance our understanding of the roles of CR and PA.

In addition, some of the mixed results throughout the literature may be due to issues within the study designs. It is important for future research to control for the energy imbalance contributed from CR, PA, or both. The study designs that have been reviewed have typically controlled for a specific per cent of decrease in caloric intake, a prescribed PA regimen (not measuring caloric expenditure), or some combination of both. We suggest that future research include CR and PA groups designed to be in a similar negative energy balance (i.e. 25% reduction in intake or 25% increase expenditure) and a CR and PA group with equivalent reductions (12.5% CR with 12.5% increase expenditure) to further investigate these interventions on cognitive performance.

Importantly, in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study, older adults (60–77 years) are being randomly assigned to a diet, exercise, cognitive training, and vascular risk monitoring group or to a control group (Ngandu et al., 2015). In this case, the diet is based upon the Finnish Nutrition Recommendations and does not include a specific focus on antioxidants, but does include recommendations for a reduction in weight of 5–10% for overweight individuals. Results from this study will hopefully contribute further to our understanding of how to best design behavioural interventions to benefit cognitive performance in older adults.

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