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Impact of Energy Intake and Expenditure on Neuronal Plasticity

Alexis M. Stranahan¹ and Mark P. Mattson^{1,*}

¹Cellular and Molecular Neuroscience Section, Laboratory of Neurosciences, National Institute on Aging Intramural Research Program

Abstract

The Roman poet Horace was among the first to recognize that when “clogged with yesterday's excess, the body drags the mind down with it.” Although considerable attention has been paid in neuroscience to the enhancement of neuronal function by wheel running and caloric restriction, far less is known about the other side of this issue. What are the consequences of unhealthy habits to central nervous system function? Prolonged exposure to excessive caloric intake impairs neuronal function, and also contributes to obesity and other risk factors for diabetes. Diabetes, a disease characterized by reduced sensitivity to glucose and insulin, is also associated with deficits in brain structure and function. In contrast, enhancement of somatic metabolism by wheel running or caloric restriction improves central neuroplasticity. Generalizing across studies reveals a relationship between global metabolic efficiency and neuroplasticity in the hippocampus, a brain region that is essential for learning and memory. The specific principles upheld by these findings are suggestive of a continuum, with global metabolic alterations fluctuating in concert with neuroplasticity in the hippocampus.

Keywords

diet; hippocampus; caloric restriction; exercise

Introduction

The hippocampus is essential for learning, memory, and mood regulation. Neurons in the hippocampus have among the highest energy requirements, as demonstrated by studies of regional glucose uptake (LaManna and Harik, 1985; McEwen and Reagan, 2004). Given their metabolic demands, it is not surprising that the function of hippocampal cells would be influenced by energy expenditure and intake (Cotman et al., 2007; Hillman et al., 2008; Lee et al., 2002). Studies using animal models have shown that excessive caloric intake is detrimental for neuronal plasticity (Molteni et al 2002), while caloric restriction enhances structural plasticity in this region (Fontan-Lozano et al 2007). Increasing energy expenditure through wheel running also enhances hippocampal structure and function (van Praag et al., 1999a, 1999b; Stranahan et al., 2006). Insulin resistant diabetes, a condition in which prolonged exposure to elevated glucose and insulin levels leads to impaired cellular responses to both factors, also exerts detrimental effects on the hippocampus (Jackson-Guilford et al., 2000; Zhang et al., 2007; Stranahan et al., 2008).

Findings from studies of human populations and clinical studies of subjects with diabetes support the hypothesis that excessive energy intake leads to deficits in neuroplasticity, while energy restriction or increased expenditure enhances neuronal function. Excessive caloric intake contributes directly to obesity, and obesity is a major risk factor for insulin resistant

* To whom correspondence should be addressed: Mark P. Mattson, mattsonm@grc.nia.nih.gov.

diabetes (Tatarinni 2000; Dandona et al., 2004). Individuals with diabetes are at increased risk for age-related cognitive impairment and Alzheimer's disease, both of which involve hippocampal atrophy (Korf et al., 2006; Pasquier et al., 2006). Although adverse effects of diabetes on the cerebral vasculature may contribute to cognitive impairment, brain imaging studies suggest that hippocampal and amygdalar atrophy occurs in diabetes regardless of vascular pathology (den Heijer et al., 2003). Individuals with relatively low dietary energy intakes are at reduced risk for Alzheimer's disease (Mayeux, 2003), whereas those who exercise regularly are protected against age-related cognitive impairment (Larson et al., 2006).

In this review, we explore the co-regulation of different mechanisms of plasticity in the adult hippocampus by energy intake and expenditure. Initially, we present neuroimaging data to suggest that caloric intake and insulin sensitivity are relevant to neuronal function and neuroendocrine stress systems in humans. Next, we discuss potential interactions between different plasticity mechanisms under baseline conditions, and under conditions of altered energy intake, cellular availability and expenditure. Lastly, we present the broader implications of a metabolic spectrum, with reference to the possibility of optimizing brain function and durability.

Neuroimaging studies

Diabetic individuals exhibit deficits in insulin production (Type 1) or impaired glucose and insulin sensitivity (Type 2). Diabetes reduces hippocampal volume, and impairs performance in behavioral tests of hippocampal function (Convit et al., 2003; Gold et al., 2007; den Heijer et al., 2003; Korf et al., 2006; but see Burns et al 2007). Obesity arises from a combination of excessive caloric intake and genetic susceptibility (Tatarinni 2000; Barsh et al., 2000). Although the mechanisms linking obesity and diabetes are still being elucidated, the association is sufficiently strong to suggest that obesity is a risk factor for diabetes (Dandona et al., 2004). Waist-to-hip ratio, an indicator of obesity, is negatively correlated with hippocampal volume in humans (Jagust et al., 2005). Functionally, obese patients exhibit reduced hippocampal activation following a liquid meal (DelParigi et al., 2004), but show increased activation following gastric distension (Wang et al., 2006). These data suggest that excessive caloric intake, combined with a genetic predisposition leading to obesity, is associated with changes in hippocampal structure and alterations in feeding-related activity in the hippocampus.

Although investigations of the relationship between exercise and brain structure in humans are scarce, preliminary studies indicate that physical activity enhances regional cerebral blood volume in the hippocampus, in parallel with improvements in declarative memory (Pereira et al., 2007). Other studies at the behavioral level have upheld this relationship (reviewed in Hillman et al., 2008). The paucity of studies surrounding the effects of caloric restriction on brain structure makes it difficult to draw conclusions about energy deficit. However, insofar as exercise and caloric restriction result in similar effects on metabolism, it is possible to suggest that caloric restriction may also promote similar changes in the hippocampus.

The spectrum of effects described above fits the concept of a continuum. A continuum is, by definition, a graded and progressive relationship. The opposing central consequences of metabolic impairment induced by diabetes and obesity, and increased metabolic efficiency induced by exercise can be considered a continuum. On one side of the balance, excessive energy intake leads to obesity, and obesity contributes to the pathogenesis of diabetes; on the other side, increased energy expenditure through exercise enhances metabolism. This sequence is recapitulated at the level of hippocampal structure and function, but the underlying mechanisms for this relationship are still being elucidated.

Hippocampus-mediated learning

The hippocampus and temporal lobe structures are critical relays for learning and memory, and studies of behavior in rodent models have contributed extensively to the elucidation of specific associational mechanisms. The Morris water maze is the most well-characterized model of hippocampus-dependent learning (Morris et al., 1986). In this paradigm, the animal swims through a pool of opaque water. Because rodents find swimming aversive, they are motivated to move through the water until they locate the hidden platform beneath its surface. While they initially locate the platform by chance, with repeated trials, they begin using visual cues to orient themselves to the platform location. This task requires allocentric encoding, because it relies on external cues; additionally, because the task requires that the animal remember the previous location where it was able to escape from the water, the water maze is thought to represent episodic-like memory in rodents (Morris 2001).

Performance in the water maze is impaired by hippocampal lesions, as well as by pharmacological, genetic, and viral-vector-induced interference with excitatory neurotransmission in the hippocampus (Nakazawa et al., 2004). Conversely, enhancement of hippocampal synaptic function by environmental and genetic manipulations also improves performance in the water maze (Maher, Akaishi and Abe 2006; Tang et al., 1999; van Praag et al., 1999b). The idea of a metabolic continuum is upheld in the literature describing impaired water maze performance in diabetic animals (Li et al., 2002; Biessels et al., 1996) and in animals maintained on a high-fat, high-glucose diet (Molteni et al., 2002); the opposite end of the spectrum is best represented by the effects of wheel running and caloric restriction, which have both been shown to enhance hippocampus-dependent memory (Fontan-Lozano et al., 2007; van Praag et al., 1999a, 1999b).

The hippocampus is also essential for object recognition memory, in both rodents and primates (Squire, Wixted and Clark 2007). Rodents show an innate bias for exploration of novel objects, and the novel object preference task takes advantage of this tendency. During training, the animal is allowed to explore two objects freely, under low-stress conditions. The objects are then removed, and some time later, the animal is presented with one familiar, and one novel object. Because the animal will then prefer to explore the novel object, the index of the percent time spent exploring the novel object provides an index of memory for the familiar one.

Object recognition memory is impaired by hippocampal lesions (Clark, Zola and Squire 2000), and enhanced by many of the same manipulations that enhance performance in the water maze (Maher, Akaishi and Abe 2006; Tang et al., 1999). However, because the animals exhibit a bias for the novel object regardless of its spatial location, this represents recognition memory, rather than memory for a spatial context. Additional distinctions between this task and the water maze are that the object preference test does not rely on aversive motivation and that, unlike the water maze, the object recognition task does not involve the formation of a novel association between a location and an action. The lack of demand for associational learning may be reflected in the fact that greater damage to the hippocampus is required in order to observe impairment in recognition memory, relative to spatial memory impairment in the water maze (Broadbent, Squire and Clark 2004). Object recognition most likely involves comparisons between the strength of firing or firing rate among different groups of neurons in the hippocampus and perirhinal cortex – although the significance of neuronal firing in terms of “familiar” versus “unfamiliar” memories, or “strong” versus “weak” memories, is still a matter of debate (Sauvage et al., 2008; Squire, Wixted and Clark 2007).

The opposing effects of diabetes and wheel running are also evident in recognition memory tasks. Diabetic animals are impaired in the novel object preference task (Stranahan et al., 2008), while running enhances recognition memory (Van der Borght 2007). No studies to date

have explored the consequences of excessive caloric intake on recognition memory. Because maintenance on a high-fat, high-glucose diet is likely to induce changes that are similar, but less severe than those observed in diabetic animals, it is possible that objection recognition memory might be spared with excessive energy intake.

Synaptic plasticity

When Timothy Bliss and Terje Lomo discovered the stable modification of synaptic strength that would come to be known as long-term potentiation (LTP; (Bliss and Lomo 1973), neuroscientists rapidly came to accept this phenomenon as a candidate cellular mechanism for learning and memory. While most research on LTP in the hippocampus has focused on the Schaffer collateral pathway between the axons from neurons in CA3 and the apical dendrites of neurons in CA1, the synapses that connect layer II stellate cells in the medial entorhinal cortex and dentate gyrus granule neurons (Figure 1) are of particular interest because this pathway represents the first excitatory input to the developing dendrites of adult-generated neurons (Schmidt-Hieber, Jonas and Bischofberger 2004). Moreover, medial perforant path LTP is enhanced by running (van Praag et al., 1999a; Farmer et al., 2004), and impaired in diabetes (Stranahan et al., 2008; Kamal et al., 1999).

Studies of excessive energy intake have focused primarily on the CA1 field, and results have been equivocal. Although there are some reports of decreased expression of proteins associated with synaptic plasticity in the hippocampus of animals fed a high-fat, high-glucose diet (Molteni et al., 2002), there was no effect of long-term excessive energy intake on CA1 LTP (Mielke et al 2006). However, it remains to be determined whether synaptic plasticity at medial perforant path synapses in the dentate gyrus might be differentially regulated by excessive caloric intake.

Paired-pulse depression is another specific characteristic of medial perforant path synapses (Asztely et al., 2000; Colino and Malenka 1993; Hanse and Gustafsson 1992). Because there is a high probability of synaptic vesicle release, the pool of available vesicles is rapidly depleted. This decreases the strength of the dendritic response when two stimuli are delivered in rapid succession. This form of short-term plasticity is not observed in the lateral perforant path, which permits the functional identification of medial perforant path synapses based on this property. Running does not influence paired-pulse depression (van Praag et al., 1999a); diabetes also did not influence this form of presynaptic plasticity (Stranahan et al., 2008). This suggests that the metabolic continuum is detectable primarily in postsynaptic mechanisms of plasticity.

Dendritic complexity and spine density

Ramon y Cajal was among the first to speculate that associational learning might induce the growth of neuronal processes (Ramon y Cajal, 1893; cited in (Yuste and Bonhoeffer 2001). Apart from his prescient statements about neuronal connectivity, Donald Hebb also suggested that changes in synaptic strength might be accompanied by alterations in neuronal morphology (Hebb 1949). Total dendritic length, as well as the complexity of the dendritic tree, can be altered by experience (Fiala, Joyce, and Greenough, 1978; Pysh and Weiss, 1979; Juraska et al., 1985; Watanabe, Gould, and McEwen 1992; Eadie, Redila and Christie 2005; Kozorovitskiy et al., 2005; Stranahan, Khalil and Gould 2007). These features influence the conductance properties of the neuron, thereby regulating its function.

Structural plasticity among dendritic spines has become accepted as an additional mechanism for learning and memory (Fedulov et al., 2007; Lang et al., 2004; Zhou, Homma and Poo 2004). The spatial and temporal pattern of spine formation closely follows that of LTP; moreover, pharmacological treatments and genetic manipulations that block LTP also block

spinogenesis (Engert and Bonhoeffer 1999). In the hippocampus, bidirectional synaptic plasticity occurs at the level of spine structure, as well as in synaptic function, because LTD has been correlated with loss and/or shrinkage of spines (Zhou, Homma and Poo 2004). If one accepts LTP as an underlying mechanism for learning and memory, then one must also accept a role for alterations in the number and structure of spines – because while the exact mechanisms of functional alterations in spine structure are still being elucidated, it is clear that these two processes are dependent on one another.

Contrasting effects of excessive energy intake and reduced energy availability are also evident in the regulation of dendritic spine density. While diabetes is associated with reduced dendritic spine density and neuronal atrophy (Magarinos and McEwen, 2000; Martinez-Tellez et al, 2005), increased energy expenditure following wheel running enhances neuronal structure (Stranahan et al 2007; Eadie and Christie 2006; Redila and Christie 2006). Caloric restriction also upregulates factors that support structural plasticity (Lee et al 2002), but data on the regulation of hippocampal neuron structure by caloric restriction remain equivocal. Although some studies have demonstrated reduced synaptic density and neuronal arborization following food restriction (Andrade et al., 2002), the diets used in these studies were low in protein, and feeding a smaller amount of a low-protein diet results in protein deficiency, which is known to inhibit synaptogenesis (Andrade et al., 1996). It remains to be determined whether caloric restriction with maintenance of adequate macronutrient content might exert different effects.

Regulation of dendritic spine morphology

Spines are morphologically heterogeneous. The shape of the spine head alters local calcium dynamics, and spine head volume is linearly correlated with the area of the post-synaptic density (Nikonenko et al., 2002). There are a number of theories regarding the importance of different spine morphologies in learning and memory; some researchers have suggested that thin, filopodia-like spines, which turn over frequently, may be critical to learning (Holtmaat et al., 2005), while other researchers suggest that larger, mushroom-headed spines may be more important (Sorra and Harris 2000, Matsuo et al., 2008).

Although the relative contributions of different morphological classes of spines are still a matter of debate, it is clear that neurons exhibit experience-dependent functional adaptations that are likely to play a role in learning and memory. Again, the opposing effects of diabetes-induced hyperglycemia, and phasic reductions in glucose levels following wheel-running, are evident in the regulation of spine structure. Diabetes reduced synaptic vesicle density at mossy fiber synapses in hippocampal area CA3 (Magarinos and McEwen 2000), while wheel running induced a bias towards longer, thinner spines in hippocampal area CA1 (Stranahan et al 2007). Additional studies of the effect of excessive energy intake and caloric restriction will be required in order to disprove or uphold the existence of a metabolic spectrum at the level of synaptic structure.

Adult neurogenesis

Ten years before Bliss and Lomo discovered LTP, Joseph Altman made the heretical suggestion that new neurons could be added to the adult brain (Altman 1962). However, compared to LTP, the phenomenon of adult neurogenesis took far longer to be accepted. The full extent of new neuron addition in the adult brain is still being explored, but within the hippocampus, the turnover of dentate gyrus granule neurons has been accepted and proposed as an additional mechanism for learning and memory (Leuner, Gould and Shors 2006).

Resident progenitor cells in the hippocampal dentate gyrus undergo asymmetric cell division, producing a transit-amplifying cell, and another progenitor. Transit amplifying cells undergo one to two additional rounds of cell division before terminal differentiation (Kempermann et

al., 2004). The estimated cell cycle duration for hippocampal progenitors in the rat is approximately 24 hours (Cameron and McKay 2001); in the mouse, cell cycle duration is approximately 14 hours (Mandyam, Harburg and Eisch 2007). Pulse-chase studies using the thymidine analog bromodeoxyuridine and double-labeling for cell-cycle stage-specific markers indicate that S-phase duration is approximately 9 hours in the rat, and 7 hours in the mouse (Cameron and McKay 2001; Hayes and Nowakowski 2002; Mandyam, Harburg and Eisch 2007).

In terms of adult neurogenesis, the consequences of running and caloric restriction are again in opposition to those of diabetes and excessive caloric intake. Running and caloric restriction enhance progenitor cell proliferation and survival, respectively, in the adult dentate gyrus (van Praag et al., 1999a, 1999b; Farmer et al 2004; Stranahan et al 2006). In contrast, diabetes and high-fat feeding inhibit the proliferation and survival of new neurons and astrocytes (Lindqvist et al., 2006; Jackson-Guilford et al., 2000; Zhang et al 2007; Stranahan et al 2008). Adult neurogenesis is a metabolically expensive process, and it is therefore not surprising that the metabolic spectrum would be observable at the level of adult neurogenesis.

Migration and maturation in newly generated neurons

New neurons migrate a short distance from the dentate subgranular zone into the dentate granule cell layer, where they extend dendrites and axons, both of which form functional contacts with medial perforant path axons and CA3 pyramidal neurons, respectively (Hastings and Gould 1999; Toni et al., 2007). The extension of processes and formation of synaptic contacts occurs during the first one to three weeks after the cell's 'birthday;' by three to four weeks post-mitosis, new neurons have fully formed dendrites and have integrated into the hippocampal circuitry (van Praag et al., 2002).

The synaptic properties of newly generated neurons recapitulate those in the developing brain. Initially, adult-generated neurons are excited by GABA (Esposito et al., 2005; Ge et al., 2006); after they transition to glutamatergic excitation, they retain a higher resting membrane potential, and exhibit greater excitability (Schmidt-Hieber, Jonas and Bischofberger 2004; Ge et al., 2007). These properties persist for the first four to six weeks, and there are reports that morphological plasticity is greater among newly generated granule neurons for up to four months after mitosis (Zhao et al., 2006). New neurons born in the brains of animals that run exhibit a higher density of large-headed spines (Zhao et al., 2006), but show synaptic functional properties that are indistinguishable from new neurons born in the brains of sedentary animals (Jakubs et al., 2006). No studies have yet investigated the effects of diabetes, excessive caloric intake, or caloric restriction on the function and morphology of newly generated neurons in the dentate gyrus.

Neuronal adaptations to caloric deficit and excess: do they reflect global metabolic changes?

The opposing effects of diabetes and running on hippocampal neuroplasticity suggest that peripheral metabolic alterations can impact the brain. Neurons are protected by the blood-brain barrier, but a variety of signals can cross the barrier, including corticosterone, insulin, and glucose, and several different growth factors and cytokines. These peripherally derived signals coordinate central adaptations, bringing central nervous system function in line with overall somatic health.

A number of candidate mechanisms have been proposed for the effects of metabolic perturbations on the brain. By comparing the literature surrounding the regulation of brain function by caloric deficit and excess, it is possible to identify common factors that may mediate

these opposing effects. The neurotrophin BDNF has been recognized as a potent modulator of neuronal excitability, synaptic function, and hippocampal morphology for over ten years. Levels of BDNF are increased by exercise and caloric restriction (Lee et al., 2002; Neeper et al., 1995), and reduced in animal models of diet-induced obesity (Molteni et al., 2002). Although BDNF also regulates energy intake, pair-feeding experiments following central administration of BDNF in insulin resistant mice indicate that effects on energy metabolism are independent of effects on energy intake (Nakagawa et al., 2000). BDNF heterozygous knockout mice are obese and insulin resistant (Duan et al., 2003), but both their diabetes and brain BDNF levels can be normalized by dietary energy restriction suggesting a functional connection between central BDNF levels and peripheral energy metabolism.

Central elevations in corticosterone suppress neuronal glucose metabolism (Sapolsky 1986), while BDNF and other neurotrophic factors exert the opposite effect (Burkhalter et al., 2003; Yeo et al., 2004). This opens the possibility that one mechanism underlying the lack of any negative consequences of exposure to running-induced elevations in corticosterone may involve neurotrophic factors. We and others have observed increases in hippocampal BDNF levels with running (Cotman, Berchtold, and Christie 2007); in fact, running has previously been demonstrated to protect against the stress-induced downregulation of BDNF (Adlard and Cotman 2004). These findings suggest that runners may be protected from the deleterious effects of exposure to elevated corticosterone levels through increases in BDNF. However, the effects of running on BDNF are likely to be secondary to changes in levels of another growth factor, insulin-like growth factor 1 (IGF-1).

Insulin-like growth factor (IGF-1) is produced in a variety of organs, including the liver, muscle, and brain (Dore, Kar, and Quirion 1997). Serum IGF-1 is reduced in animal models of insulin-deficient and insulin-resistant diabetes (Kim et al., 2006; Kumari et al., 2007); in contrast, running and caloric restriction both enhance production of IGF-1 (Niedernhofer et al., 2006; Carro et al., 2001). A causal relationship for running-induced alterations in serum IGF-1 and hippocampal neurogenesis was proposed, based on experiments using peripheral blockade of IGF-1 (Trejo, Carro, and Torres-Aleman 2001). Administration of exogenous IGF-1 ameliorates cognitive deficits in diabetic animals, and enhances hippocampal learning in non-diabetic animals (Lupien, Bluhm, and Ishii 2003). Additionally, the effects of running on hippocampal BDNF levels are prevented when peripheral upregulation of IGF-1 is blocked (Chen and Russo-Neustadt 2007). Thus, it is possible that alterations in IGF-1 may be upstream of BDNF in the opposing effects of caloric excess and deficit in the hippocampus.

Conclusion

The studies presented in this review are meant to explore the relationship between global somatic energy metabolism, hippocampal neuroplasticity, and behavioral alterations in learning and memory. The overall trend of these findings supports a continuum, with diabetes- and stress-induced impairments on the low end, and running-induced enhancement at the higher end. This continuum was observable across a variety of structural, synaptic, behavioral, and biochemical measures. The relationship between central nervous system function and global energy metabolism has been described in terms of 'allostatic load,' by Bruce McEwen; 'allostasis' is a process in which the sum of the competing mediators of enhanced and impaired cognitive function determines the outcome (2001). While the direction of the findings described above fits well with the theory of allostasis, a number of questions remain regarding the mechanisms and brain regions that are sensitive to the opposing effects of diabetes and wheel running.

Most studies of the association between cardiovascular fitness and cognition in humans have observed improvement on tasks typically related to prefrontal and cortical structures (Hillman,

Erickson, and Kramer 2008). Similar correlations have been observed for glycemic control and cognition; most of the reported deficits in the human literature involve working memory and executive function (Messier 2005). However, the bulk of the studies in animal models have focused on the hippocampus. It would be interesting and relevant to evaluate whether the opposing effects of exercise and diabetes represent a general phenomenon in the brain, or whether this relationship is specific to the hippocampus.

Running and diabetes also oppose each other in regulating disease progression across a number of neurodegenerative disorders. In humans, regular cardiovascular exercise is correlated with reduced risk of Alzheimer's dementia (Cotman, Berchtold, and Christie 2007; Hillman, Erickson, and Kramer 2008); in contrast, type 2 diabetes is correlated with increased risk (Messier 2005). In animal models, running and caloric restriction attenuate the accumulation of amyloid-beta in animal models (Adlard et al., 2005; Halagappa et al., 2007; but see Wolf et al., 2006, for an alternative viewpoint on the time-dependence of the effects of wheel running on A β plaque accumulation), while diet-induced insulin resistance accelerates disease progression (Ho et al., 2004). Elevations in corticosterone levels also contribute to Alzheimer's disease progression (Green et al., 2006), and it would be worthwhile to determine whether running-induced elevations in corticosterone levels might act as a pre-conditioning mechanism in animal models of neurodegenerative disease.

The regional extent and mechanisms for the opposing effects of exercise and diabetes are still being characterized. Understanding the relationship between energy metabolism and plasticity in the central nervous system has significant implications for understanding human brain development, aging, and disease. Given the explosion in juvenile-onset insulin resistance, (Bloomgarden 2004) it would be relevant assess whether the results observed in the adult brain might be exacerbated or attenuated at other points during the lifespan. Identifying and characterizing relationships between peripherally derived metabolic signals and plasticity will help to further an integrated theory of somatic and cognitive functioning.

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References

- Adlard PA, Cotman CW. Voluntary exercise protects against stress-induced decreases in brain-derived neurotrophic factor protein expression. *Neuroscience* 2004;124:985–992. [PubMed: 15026138]
- Adlard PA, Perreau VM, Pop V, Cotman CW. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. *J Neurosci* 2005;25:4217–4221. [PubMed: 15858047]
- Altman J. Are new neurons formed in the brains of adult mammals? *Science* Mar 30;1962 135:1127–8. [PubMed: 13860748]
- Andrade JP, Lukoyanov NV, Paula-Barbosa MM. Chronic food restriction is associated with subtle dendritic alterations in granule cells of the rat hippocampal formation. *Hippocampus* 2002;12:149–64. [PubMed: 12000115]
- Andrade JP, Castanheira-Vale AJ, Paz-Dias PG, Madeira MD, Paula-Barbosa MM. The dendritic trees of neurons from the hippocampal formation of protein-deprived adult rats. A quantitative Golgi study. *Exp Brain Res* 1996;109:419–33. [PubMed: 8817272]
- Asztely F, Kokaia M, Olofsdotter K, Ortegren U, Lindvall O. Afferent-specific modulation of short-term synaptic plasticity by neurotrophins in dentate gyrus. *Euro J Neurosci* 2000;12:662–669.
- Barsh GS, Farooqi IS, O'Rahilly S. Genetics of body-weight regulation. *Nature* 2000;404:644–651. [PubMed: 10766251]

- Biessels GJ, Kamal A, Ramakers GM, Urban IJ, Spruijt BM, Erkelens DW, Gispen WH. Place learning and hippocampal synaptic plasticity in streptozotocin-induced diabetic rats. *Diabetes Sep*;1996 45(9): 1259–66. [PubMed: 8772732]
- Bliss TV, Lomo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J Physiol* 1973;232:331–356. [PubMed: 4727084]
- Bloomgarden ZT. Type 2 diabetes in the young: the evolving epidemic. *Diabetes Care* 2004;27:998–1010. [PubMed: 15047665]
- Broadbent NJ, Squire LR, Clark RE. Spatial memory, recognition memory, and the hippocampus. *Proc Natl Acad Sci U S A* 2004;101:14515–14520. [PubMed: 15452348]
- Burkhalter J, Fiumelli H, Allaman I, Chatton JY, Martin JL. Brain-derived neurotrophic factor stimulates energy metabolism in developing cortical neurons. *J Neurosci* 2003;23:8212–8220. [PubMed: 12967982]
- Burns JM, Donnelly JE, Anderson HS, Mayo MS, Spencer-Gardner L, Thomas G, Cronk BB, Haddad Z, Klima D, Hansen D, Brooks WM. Peripheral insulin and brain structure in early Alzheimer disease. *Neurology* 2007;69:1094–1104. [PubMed: 17846409]
- Cameron HA, McKay RD. Adult neurogenesis produces a large pool of new granule cells in the dentate gyrus. *J Comp Neurol* 2001;435:406–417. [PubMed: 11406822]
- Carro E, Trejo JL, Busiguina S, Torres-Aleman I. Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. *J Neurosci* 2001;21:5678–5684. [PubMed: 11466439]
- Chen MJ, Russo-Neustadt AA. Running exercise- and antidepressant-induced increases in growth and survival-associated signaling molecules are IGF-dependent. *Growth Factors* 2007;25:118–131. [PubMed: 17852404]
- Clark RE, Zola SM, Squire LR. Impaired recognition memory in rats after damage to the hippocampus. *J Neurosci* 2000;20:8853–8860. [PubMed: 11102494]
- Colino A, Malenka RC. Mechanisms underlying induction of long-term potentiation in rat medial and lateral perforant paths in vitro. *J Neurophysiol* 1993;69:1150–1159. [PubMed: 8492154]
- Convit A, Wolf OT, Tarshish C, de Leon MJ. Reduced glucose tolerance is associated with poor memory performance and hippocampal atrophy among normal elderly. *Proc Natl Acad Sci U S A* 2003;100:2019–2022. [PubMed: 12571363]
- Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health, key roles of growth factor cascades and inflammation. *Trends Neurosci* 2007;30:464–472. [PubMed: 17765329]
- Dandona P, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. *Trends in Immunology* 2004;25(1):4–7. [PubMed: 14698276]
- DelParigi A, Chen K, Salbe AD, Hill JO, Wing RR, Reiman EM, Tataranni PA. Persistence of abnormal neural responses to a meal in postobese individuals. *Int J Obes Relat Metab Disord* Mar;2004 28(3): 370–7. [PubMed: 14676847]
- den Heijer T, Vermeer SE, van Dijk EJ, Prins ND, Koudstaal PJ, Hofman A, Breteler MM. Type 2 diabetes and atrophy of medial temporal lobe structures on brain. MRI. *Diabetologia* 2003;46:1604–1610. [PubMed: 14595538]
- Dore S, Kar S, Quirion R. Rediscovering an old friend, IGF-I, potential use in the treatment of neurodegenerative diseases. *Trends Neurosci* 1997;20:326–331. [PubMed: 9246719]
- Duan W, Guo Z, Jiang H, Ware M, Mattson MP. Reversal of behavioral and metabolic abnormalities, and insulin resistance syndrome, by dietary restriction in mice deficient in brain-derived neurotrophic factor. *Endocrinology* 2003;144:2446–2453. [PubMed: 12746306]
- Eadie BD, Redila VA, Christie BR. Voluntary exercise alters the cytoarchitecture of the adult dentate gyrus by increasing cellular proliferation, dendritic complexity, and spine density. *J Comp Neurol* 2005;486:39–47. [PubMed: 15834963]
- Engert F, Bonhoeffer T. Dendritic spine changes associated with hippocampal long-term synaptic plasticity. *Nature* 1999;399:66–70. [PubMed: 10331391]
- Esposito MS, Piatti VC, Laplagne DA, Morgenstern NA, Ferrari CC, Pitossi FJ, Schinder AF. Neuronal differentiation in the adult hippocampus recapitulates embryonic development. *J Neurosci* 2005;25:10074–10086. [PubMed: 16267214]

- Farmer J, Zhao X, van Praag H, Wodtke K, Gage FH, Christie BR. Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. *Neuroscience* 2004;124:71–79. [PubMed: 14960340]
- Fedulov V, Rex CS, Simmons DA, Palmer L, Gall CM, Lynch G. Evidence that long-term potentiation occurs within individual hippocampal synapses during learning. *J Neurosci* 2007;27:8031–8039. [PubMed: 17652593]
- Fiala BA, Joyce JN, Greenough WT. Environmental complexity modulates growth of granule cell dendrites in developing but not adult hippocampus of rats. *Exp Neurol* 1978;59:372–83. [PubMed: 648609]
- Fontán-Lozano A, Sáez-Cassanelli JL, Inda MC, de los Santos-Arteaga M, Sierra-Domínguez SA, López-Lluch G, Delgado-García JM, Carrión AM. Caloric restriction increases learning consolidation and facilitates synaptic plasticity through mechanisms dependent on NR2B subunits of the NMDA receptor. *J Neurosci* 2007;27:10185–95. [PubMed: 17881524]
- Ge S, Goh EL, Sailor KA, Kitabatake Y, Ming GL, Song H. GABA regulates synaptic integration of newly generated neurons in the adult brain. *Nature* 2006;439:589–593. [PubMed: 16341203]
- Ge S, Yang CH, Hsu KS, Ming GL, Song H. A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. *Neuron* 2007;54:559–566. [PubMed: 17521569]
- Gold SM, Dziobek I, Sweat V, Tirsi A, Rogers K, Bruehl H, Tsui W, Richardson S, Javier E, Convit A. Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. *Diabetologia* 2007;50:711–719. [PubMed: 17334649]
- Green KN, Billings LM, Roozendaal B, McGaugh JL, LaFerla FM. Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. *J Neurosci* 2006;26:9047–9056. [PubMed: 16943563]
- Halagappa VK, Guo Z, Pearson M, Matsuoka Y, Cutler RG, Laferla FM, Mattson MP. Intermittent fasting and caloric restriction ameliorate age-related behavioral deficits in the triple-transgenic mouse model of Alzheimer's disease. *Neurobiol Dis* 2007;26:212–220. [PubMed: 17306982]
- Hanse E, Gustafsson B. Long-term Potentiation and Field EPSPs in the Lateral and Medial Perforant Paths in the Dentate Gyrus In Vitro, a Comparison. *Eur J Neurosci* 1992;4:1191–1201. [PubMed: 12106423]
- Hastings NB, Gould E. Rapid extension of axons into the CA3 region by adult-generated granule cells. *J Comp Neurol* 1999;413:146–154. [PubMed: 10464376]
- Hayes NL, Nowakowski RS. Dynamics of cell proliferation in the adult dentate gyrus of two inbred strains of mice. *Brain Res Dev Brain Res* 2002;134:77–85.
- Hebb, DO. *The Organization of Behavior: A Neuropsychological Theory*. John Wiley and Sons, Inc.; New York: 1949.
- Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart, exercise effects on brain and cognition. *Nat Rev Neurosci* 2008;9:58–65. [PubMed: 18094706]
- Ho L, Qin W, Pompl PN, Xiang Z, Wang J, Zhao Z, Peng Y, Cambareri G, Rocher A, Mobbs CV, Hof PR, Pasinetti GM. Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer's disease. *FASEB J* 2004;18:902–904. [PubMed: 15033922]
- Holtmaat AJ, Trachtenberg JT, Wilbrecht L, Shepherd GM, Zhang X, Knott GW, Svoboda K. Transient and persistent dendritic spines in the neocortex in vivo. *Neuron* 2005;45:279–291. [PubMed: 15664179]
- Jackson-Guilford J, Leander JD, Nisenbaum LK. The effect of streptozotocin-induced diabetes on cell proliferation in the rat dentate gyrus. *Neurosci Lett* 2000;293:91–94. [PubMed: 11027841]
- Jagust W, Harvey D, Mungas D, Haan M. Central obesity and the aging brain. *Arch Neurol* Oct;2005 62 (10):1545–8. [PubMed: 16216937]
- Jakubs K, Nanobashvili A, Bonde S, Ekdahl CT, Kokaia Z, Kokaia M, Lindvall O. Environment matters, synaptic properties of neurons born in the epileptic adult brain develop to reduce excitability. *Neuron* 2006;52:1047–59. [PubMed: 17178407]
- Juraska JM, Fitch JM, Henderson C, Rivers N. Sex differences in dendritic branching of dentate granule cells following differential experience. *Brain Res* 1985;333:73–80. [PubMed: 3995290]

- Kamal A, Biessels GJ, Urban JJ, Gispen WH. Hippocampal synaptic plasticity in streptozotocin-diabetic rats, impairment of long-term potentiation and facilitation of long-term depression. *Neuroscience* 1999;90:737–45. [PubMed: 10218775]
- Kempermann G, Jessberger S, Steiner B, Kronenberg G. Milestones of neuronal development in the adult hippocampus. *Trends Neurosci* 2004;27:447–452. [PubMed: 15271491]
- Kim E, Sohn S, Lee M, Jung J, Kineman RD, Park S. Differential responses of the growth hormone axis in two rat models of streptozotocin-induced insulinopenic diabetes. *J Endocrinol* 2006;188:263–270. [PubMed: 16461552]
- Korf ES, White LR, Scheltens P, Launer LJ. Brain aging in very old men with type 2 diabetes, the Honolulu-Asia Aging Study. *Diabetes Care* 2006;29:2268–2274. [PubMed: 17003305]
- Kozorovitskiy Y, Gross CG, Kopil C, Battaglia L, McBreen M, Stranahan AM, Gould E. Experience induces structural and biochemical changes in the adult primate brain. *Proc Natl Acad Sci U S A* 2005;102:17478–17482. [PubMed: 16299105]
- Kumari R, Willing LB, Krady JK, Vannucci SJ, Simpson IA. Impaired wound healing after cerebral hypoxia-ischemia in the diabetic mouse. *J Cereb Blood Flow Metab* 2007;27:710–718. [PubMed: 16926846]
- LaManna JC, Harik SI. Regional comparisons of brain glucose influx. *Brain Res* 1985;326:299–305. [PubMed: 3971156]
- Lang C, Barco A, Zablow L, Kandel ER, Siegelbaum SA, Zakharenko SS. Transient expansion of synaptically connected dendritic spines upon induction of hippocampal long-term potentiation. *Proc Natl Acad Sci U S A* 2004;101:16665–16670. [PubMed: 15542587]
- Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, Kukull W. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Ann Intern Med* 2006;144:73–81. [PubMed: 16418406]
- Lee J, Duan W, Mattson MP. Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. *J Neurochem* 2002;82:1367–1375. [PubMed: 12354284]
- Leuner B, Gould E, Shors TJ. Is there a link between adult neurogenesis and learning? *Hippocampus* 2006;16:216–224. [PubMed: 16421862]
- Li XL, Aou S, Oomura Y, Hori N, Fukunaga K, Hori T. Impairment of long-term potentiation and spatial memory in leptin receptor-deficient rodents. *Neuroscience* 2002;113:607–615. [PubMed: 12150780]
- Lindqvist A, Mohapel P, Bouter B, Frielingsdorf H, Pizzo D, Brundin P, Erlanson-Albertsson C. High-fat diet impairs hippocampal neurogenesis in male rats. *Eur J Neurol* 2006;13:1385–8. [PubMed: 17116226]
- Lupien SB, Bluhm EJ, Ishii DN. Systemic insulin-like growth factor-I administration prevents cognitive impairment in diabetic rats, and brain IGF regulates learning/memory in normal adult rats. *J Neurosci Res* 2003;74:512–523. [PubMed: 14598295]
- Magarinos AM, McEwen BS. Experimental diabetes in rats causes hippocampal dendritic and synaptic reorganization and increased glucocorticoid reactivity to stress. *Proc Natl Acad Sci U S A* 2000;97:11056–11061. [PubMed: 11005876]
- Maher P, Akaishi T, Abe K. Flavonoid fisetin promotes ERK-dependent long-term potentiation and enhances memory. *Proc Natl Acad Sci U S A* 2006;103:16568–16573. [PubMed: 17050681]
- Mandyam CD, Harburg GC, Eisch AJ. Determination of key aspects of precursor cell proliferation, cell cycle length and kinetics in the adult mouse subgranular zone. *Neuroscience* 2007;146:108–122. [PubMed: 17307295]
- Martínez-Tellez R, Gómez-Villalobos Mde J, Flores G. Alteration in dendritic morphology of cortical neurons in rats with diabetes mellitus induced by streptozotocin. *Brain Res* 2005;1048:108–15. [PubMed: 15916754]
- Matsuo N, Reijmers L, Mayford M. Spine-type-specific recruitment of newly synthesized AMPA receptors with learning. *Science* Feb 22;2008 319(5866):1104–7. [PubMed: 18292343]
- Mayeux R. Epidemiology of neurodegeneration. *Annu Rev Neurosci* 2003;26:81–104. [PubMed: 12574495]
- McEwen BS. Plasticity of the hippocampus: adaptation to chronic stress and allostatic load. *Ann N Y Acad Sci* Mar;2001 933:265–77. [PubMed: 12000027]

- McEwen BS, Reagan LP. Glucose transporter expression in the central nervous system, relationship to synaptic function. *European Journal of Pharmacology* 2004;490:13–24. [PubMed: 15094070]
- Messier C. Impact of impaired glucose tolerance and type 2 diabetes on cognitive aging. *Neurobiol Aging* 2005;26(Suppl 1):26–30. [PubMed: 16236384]
- Mielke JG, Nicolitch K, Avellaneda V, Earlam K, Ahuja T, Mealing G, Messier C. Longitudinal study of the effects of a high-fat diet on glucose regulation, hippocampal function, and cerebral insulin sensitivity in C57BL/6 mice. *Behav Brain Res* Dec 15;2006 175(2):374–82. [PubMed: 17081630]
- Molteni R, Barnard RJ, Ying Z, Roberts CK, Gomez-Pinilla F. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. *Neuroscience* 2002;112:803–814. [PubMed: 12088740]
- Morris RG. Episodic-like memory in animals, psychological criteria, neural mechanisms and the value of episodic-like tasks to investigate animal models of neurodegenerative disease. *Philos Trans R Soc Lond B Biol Sci* 2001;356:1453–1465. [PubMed: 11571036]
- Morris RG, Anderson E, Lynch GS, Baudry M. Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. *Nature* 1986;319:774–776. [PubMed: 2869411]
- Nakagawa T, Tsuchida A, Itakura Y, Nonomura T, Ono M, Hirota F, Inoue T, Nakayama C, Taiji M, Noguchi H. Brain-derived neurotrophic factor regulates glucose metabolism by modulating energy balance in diabetic mice. *Diabetes* 2000;49:436–444. [PubMed: 10868966]
- Nakazawa K, McHugh TJ, Wilson MA, Tonegawa S. NMDA receptors, place cells and hippocampal spatial memory. *Nat Rev Neurosci* 2004;5:361–372. [PubMed: 15100719]
- Neeper SA, Gomez-Pinilla F, Choi J, Cotman C. Exercise and brain neurotrophins. *Nature* 1995;373:109. [PubMed: 7816089]
- Neeper SA, Gomez-Pinilla F, Choi J, Cotman CW. Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. *Brain Res* 1996;726:49–56. [PubMed: 8836544]
- Niedernhofer LJ, Garinis GA, Raams A, Lalai AS, Robinson AR, Appeldoorn E, Odijk H, Oostendorp R, Ahmad A, van Leeuwen W, Theil AF, Vermeulen W, van der Horst GT, Meinecke P, Kleijer WJ, Vijg J, Jaspers NG, Hoeijmakers JH. A new progeroid syndrome reveals that genotoxic stress suppresses the somatotroph axis. *Nature* 2006;444:1038–43. [PubMed: 17183314]
- Nikonenko I, Jourdain P, Alberi S, Toni N, Muller D. Activity-induced changes of spine morphology. *Hippocampus* 2002;12:585–591. [PubMed: 12440574]
- Oladehin A, Waters RS. Location and distribution of Fos protein expression in rat hippocampus following acute moderate aerobic exercise. *Exp Brain Res* 2001;137:26–35. [PubMed: 11310169]
- Pasquier F, Boulogne A, Leys D, Fontaine P. Diabetes mellitus and dementia. *Diabetes Metab* 2006;32:403–414. [PubMed: 17110895]
- Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, Sloan R, Gage FH, Brown TR, Small SA. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc Natl Acad Sci U S A* 2007;104:5638–5643. [PubMed: 17374720]
- Pysh JJ, Weiss M. Exercise during development induces an increase in Purkinje cell dendritic tree size. *Science* 1979;206:230–32. [PubMed: 482938]
- Redila VA, Christie BR. Exercise-induced changes in dendritic structure and complexity in the adult hippocampal dentate gyrus. *Neuroscience* 2006;137:1299–1307. [PubMed: 16338077]
- Rhodes JS, Garland T Jr, Gammie SC. Patterns of brain activity associated with variation in voluntary wheel-running behavior. *Behav Neurosci* 2003;117:1243–1256. [PubMed: 14674844]
- Sapolsky RM. Glucocorticoid toxicity in the hippocampus, reversal by supplementation with brain fuels. *J Neurosci* 1986;6:2240–2244. [PubMed: 3746406]
- Sauvage MM, Fortin NJ, Owens CB, Yonelinas AP, Eichenbaum H. Recognition memory, opposite effects of hippocampal damage on recollection and familiarity. *Nat Neurosci* 2008;11:16–18. [PubMed: 18037884]
- Schmidt-Hieber C, Jonas P, Bischofberger J. Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. *Nature* 2004;429:184–187. [PubMed: 15107864]
- Sima AA, Li ZG. The effect of C-peptide on cognitive dysfunction and hippocampal apoptosis in type 1 diabetic rats. *Diabetes* 2005;54:1497–1505. [PubMed: 15855338]

- Sorra KE, Harris KM. Overview on the structure, composition, function, development, and plasticity of hippocampal dendritic spines. *Hippocampus* 2000;10:501–511. [PubMed: 11075821]
- Squire LR, Wixted JT, Clark RE. Recognition memory and the medial temporal lobe, a new perspective. *Nat Rev Neurosci* 2007;8:872–883. [PubMed: 17948032]
- Stranahan AM, Khalil D, Gould E. Running induces widespread structural alterations in the hippocampus and entorhinal cortex. *Hippocampus* 2007;17:1017–1022. [PubMed: 17636549]
- Stranahan AM, Khalil D, Gould E. Social isolation delays the positive effects of running on adult neurogenesis. *Nat Neurosci* 2006;9:526–533. [PubMed: 16531997]
- Stranahan AM, Arumugam TV, Cutler RG, Lee K, Egan JM, Mattson MP. Diabetes impairs hippocampal function through glucocorticoid-mediated effects on new and mature neurons. *Nat Neurosci* Mar; 2008 11(3):309–317. [PubMed: 18278039]
- Tang YP, Shimizu E, Dube GR, Rampon C, Kerchner GA, Zhuo M, Liu G, Tsien JZ. Genetic enhancement of learning and memory in mice. *Nature* 1999;401:63–69. [PubMed: 10485705]
- Tataranni PA. Mechanisms of weight gain in humans. *Eur Rev Med Pharmacol Sci* 2000;4:1–7. [PubMed: 11409183]
- Toni N, Teng EM, Bushong EA, Aimone JB, Zhao C, Consiglio A, van Praag H, Martone ME, Ellisman MH, Gage FH. Synapse formation on neurons born in the adult hippocampus. *Nat Neurosci* 2007;10:727–734. [PubMed: 17486101]
- Trejo JL, Carro E, Torres-Aleman I. Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. *J Neurosci* 2001;21:1628–1634. [PubMed: 11222653]
- Van der Borght K, Havekes R, Bos T, Eggen BJ, Van der Zee EA. Exercise improves memory acquisition and retrieval in the Y-maze task: relationship with hippocampal neurogenesis. *Behav Neurosci* 2007;121:324–34. [PubMed: 17469921]
- van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci U S A* 1999a;96:13427–13431. [PubMed: 10557337]
- van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci* 1999b;2:266–270. [PubMed: 10195220]
- van Praag H, Schinder AF, Christie BR, Toni N, Palmer TD, Gage FH. Functional neurogenesis in the adult hippocampus. *Nature* 2002;415:1030–1034. [PubMed: 11875571]
- Wang GJ, Yang J, Volkow ND, Telang F, Ma Y, Zhu W, Wong CT, Tomasi D, Thanos PK, Fowler JS. Gastric stimulation in obese subjects activates the hippocampus and other regions involved in brain reward circuitry. *Proc Natl Acad Sci U S A* Oct 17;2006 103(42):15641–5. [PubMed: 17023542]
- Watanabe Y, Gould E, McEwen BS. Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. *Brain Res* 1992;588:341–5. [PubMed: 1393587]
- Wolf SA, Kronenberg G, Lehmann K, Blankenship A, Overall R, Staufenbiel M, Kempermann G. Cognitive and physical activity differently modulate disease progression in the amyloid precursor protein (APP)-23 model of Alzheimer's disease. *Biol Psychiatry* Dec 15;2006 60(12):1314–23. [PubMed: 16806094]
- Yeo GS, Connie Hung CC, Rochford J, Keogh J, Gray J, Sivaramakrishnan S, O'Rahilly S, Farooqi IS. A de novo mutation affecting human TrkB associated with severe obesity and developmental delay. *Nat Neurosci* 2004;7:1187–1189. [PubMed: 15494731]
- Yuste R, Bonhoeffer T. Morphological changes in dendritic spines associated with long-term synaptic plasticity. *Annu Rev Neurosci* 2001;24:1071–1089. [PubMed: 11520928]
- Zhang WJ, Tan YF, Yue JT, Vranic M, Wojtowicz JM. Impairment of hippocampal neurogenesis in streptozotocin-treated diabetic rats. *Acta Neurol Scand* 2008;117:205–10. [PubMed: 17854417]
- Zhao C, Teng EM, Summers RG Jr, Ming GL, Gage FH. Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. *J Neurosci* 2006;26:3–11. [PubMed: 16399667]
- Zhou Q, Homma KJ, Poo MM. Shrinkage of dendritic spines associated with long-term depression of hippocampal synapses. *Neuron* 2004;44:749–757. [PubMed: 15572107]
- Zhou J, Wang L, Ling S, Zhang X. Expression changes of growth-associated protein-43 (GAP-43) and mitogen-activated protein kinase phosphatase-1 (MKP-1) and in hippocampus of streptozotocin-induced diabetic cognitive impairment rats. *Exp Neurol* Aug;2007 206(2):201–8. [PubMed: 17601561]

Figure 1. Opposing effects of running and diabetes in the hippocampal CA1 field and dentate gyrus

(A) There have been multiple examples in the literature of opposite effects for running and diabetes in hippocampal area CA1. These findings are summarized in the green box (left), for the effects of running; and in the orange box (right), for the effects of diabetes. (B), Schematic diagram of hippocampal anatomy. Pathways excluded from this diagram include the associational-commisural pathway, the direct connection between perforant path axons and area CA3; and the afferent projections of CA1 neurons to the subiculum and layer V entorhinal cortical pyramidal neurons. (C), Opposing effects of running (left green box) and diabetes (right orange box) in the dentate gyrus of the hippocampus. Abbreviations: EC=entorhinal cortex, DG=dentate gyrus, LPP=lateral perforant path, MPP=medial perforant path, MF=mossy fibers, SC=Schaffer collaterals.

Figure 2. Opposite effects of running and diabetes on mechanisms of plasticity in the adult hippocampus

(A), In rodents that run, corticosterone levels are elevated. However, the enhancement of adult neurogenesis, synaptic plasticity, and dendritic arborization by running occurs despite elevated corticosterone levels. Enhancement of hippocampal structural plasticity is one mechanism for improved performance on hippocampus-dependent memory tasks following running. (B), In diabetic animals, elevated corticosterone levels are accompanied by reduced production of neurotrophic factors (although it remains to be determined whether diabetes-induced suppression of hippocampal growth factor expression is due to elevated corticosterone levels). Increased corticosterone and reduced neurotrophins are both likely contributors to the impairment of adult neurogenesis, synaptic plasticity, and dendritic spine density in the hippocampus of diabetic rodents. These structural changes probably mediate alterations in hippocampus-dependent memory that we and others have observed in diabetic mice and rats (Stranahan et al., 2008). Dashed lines (---) indicate correlative relationships that have not yet been causally investigated in the context of running and diabetes.