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The impact of diet-based glycaemic response and glucose regulation on cognition: evidence across the lifespan.

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3　The impact of diet-based glycaemic response and glucose regulation on cognition: evidence

4　across the lifespan.

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11

12　Abstract

13　The brain has a high metabolic rate and its metabolism is almost entirely restricted to

14　oxidative utilization of glucose. These factors emphasize the extreme dependence of neural

15　tissue on a stable and adequate supply of glucose. Whereas initially it was thought that only

16　glucose deprivation (i.e. under hypoglycaemic conditions) can affect brain function it has

17　become apparent that low-level fluctuations in central availability can affect neural and

18　consequently, cognitive performance. In this paper the impact of diet-based glycaemic

19　response and glucose regulation on cognitive processes across the life span will be

20　reviewed. The data suggest that although an acute rise in blood glucose levels has some

21　short-term improvements of cognitive function, a more stable blood glucose profile which

22　avoids greater peaks and troughs in circulating glucose is associated with better cognitive

23　function and a lower risk of cognitive impairments in the longer term. Therefore, a habitual

24　diet that secures optimal glucose delivery to the brain in the fed and fasting states should be

25　most advantageous for the maintenance of cognitive function. Although the evidence to

26　date is promising, it is insufficient to allow firm and evidence-based nutritional

27　recommendations. What limits our ability to draw strong conclusions from the findings of

28　previous studies is the fact that they often differ widely with respect to subject

29　characteristics and cognitive tests used. Future research needs to carefully consider

30　conceptual and methodological factors including potential inter-individual differences,

31　adequate selection of tests and control of extraneous (confounding) variables. The rise in

32　obesity, diabetes and metabolic syndrome in recent years highlights the need for targeted

1

33   dietary and lifestyle strategies to promote healthy lifestyle and brain function across the

34   lifespan and for future generations. Consequently, there is an urgent need for hypothesis-

35   driven, randomised controlled trials that evaluate the role of different glycaemic

36   manipulations on cognition.

37

38   **Background**

39   Rise in nutrition-related illness highlights the need for targeted health promotion and

40   interventions across the lifespan and for future generations. Traditionally the focus of such

41   interventions was on development of chronic disease and premature death. However, there

42   is now a large body of evidence demonstrating that cognitive decline accompanies certain

43   metabolic health conditions such as type 2 diabetes, metabolic syndrome and obesity and

44   that modifiable lifestyle factors including diet may contribute significantly to the risk of

45   cognitive decline, including dementia[1]. Consequently, there has been increasing interest in

46   the effects of nutrition on cognitive performance and more specifically how cognitive

47   performance can be optimised using nutritional interventions. When looking across the life-

48   span, broadly speaking nutritional interventions offer opportunity to i) optimize cognitive

49   development during infancy and childhood, ii) ensure the highest levels of cognitive function

50   during adulthood and iii) prevent cognitive decline in older age (see Figure 1).

51

52   The macronutrient glucose is perhaps most thoroughly researched in terms of its effects on

53   cognition. Investigations into the effects of glucose on cognition have served as a useful

54   prototype to develop paradigms for studying the effects of more complex nutrition-like

55   interventions. The notion that oral glucose administration might facilitate mental

56   performance was first proposed in the 1950's. Hafermann[2] investigated the effects of

57   glucose administration on school children, and observed a distinct increase in cognitive

58   performance, including performance in mathematics and generally improved concentration.

59   However, it was not until the mid 1980's that glucose effects on cognitive performance

60   became more widely investigated[3]. Here the impact of diet-based glycaemic response and

61   glucose regulation on cognitive processes across the life span will be reviewed. Before

62   considering the relationship of glucose, glycaemic response and cognitive processes, some

63   features of glucose metabolism important for the understanding of its role in cognition will

64   be discussed.

2

65

66

67   **Glucose: the major source of energy for the brain**

68   The central significance of glucose as the major nutrient of the brain, its metabolism and

69   control, have been well documented. All processes of cells (including nerve cells) require

70   energy. In humans and most animals, adenosine triphosphate (ATP) works as the main

71   carrier of chemical energy. The human body uses three types of molecules to yield the

72   necessary energy to drive ATP synthesis: fats, proteins, and carbohydrates. In addition to

73   being the major source of biological energy, aerobic carbohydrate metabolism is the main

74   source of energy available for brain tissue and glucose and oxygen are the sole metabolic

75   energy source that can cross the blood brain barrier and hence be utilized by brain cells to

76   form ATP[4]. Brain tissue is absolutely dependent upon the oxidative metabolism of glucose

77   for energy as glucose is essentially the sole energy fuel for the brain except during

78   prolonged starvation when ketone bodies, generated by the liver, replace glucose[5].

79   Associated measurements of oxygen and glucose levels in blood sampled upon entering and

80   leaving the brain in humans show that almost all the oxygen utilised by the brain can be

81   accounted for by the oxidative metabolism of glucose[6]. Compared with other organs, the

82   brain possesses paradoxically limited stores of glycogen, which without replenishment are

83   exhausted in up to 10 minutes. In nervous tissue, glycogen is stored in astrocytes. Astrocytes

84   participate significantly in brain glucose uptake and metabolism and due to their location

85   and metabolic versatility; they may be the "fuel processing plants" within the central

86   nervous system[7] . Due to limited glycogen storage capacity, the brain relies on a continuous

87   supply of glucose as its primary fuel, delivered via the bloodstream. The entry of glucose

88   into the brain is mediated by the family of glucose (GLUT) transporters which are adapted to

89   the metabolic needs of the tissue in which it is found. The primary GLUT isoforms in the

90   brain are GLUT1 and GLUT3 but others have been detected in different brain regions, at a

91   lower level of expression[8].

92

93   The immense expenditure of energy by the brain relative to its weight and volume is

94   thought to be due to the need to maintain ionic gradients across the neuronal membrane,

95   on which the conduction of impulses in the billions of neurons. In addition, there is no break

96   from the brain's energy demand as the rate of brain metabolism is relatively steady day and

3

97   night, and may even increase slightly during the dreaming phases of sleep. Thus the energy

98   requirements of brain tissue are exceptionally constant[9] and glucose deprivation can

99   severely disrupt neuronal activity, producing EEG patterns characteristic of lowered

100 cognitive functioning[10]. Indeed, when blood glucose drops below 4 mmol/l (72 mg/dl;

101 hypoglycaemic condition), it can cause discomfort, confusion, coma, convulsions, or even

102 death in extreme conditions[11]. Conversely, persistent blood glucose concentrations above

103 the normal range (hyperglycaemic condition) can also have damaging physiological effects.

104 Because glucose exerts osmotic pressure in the extracellular fluid, extremely high blood

105 glucose concentrations can cause cellular dehydration. An excessively high level of blood

106 glucose concentration also causes loss of glucose in the urine, which can affect kidney

107 function and deplete the body's supply of fluids and electrolytes[12].

108

109 **Glucose brain metabolism: changes across the lifespan**

110 The rate of glucose brain metabolism changes across the life span. Initially, there is a rise in

111 the rate of glucose utilization from birth until about age 4 years, at which time the child's

112 cerebral cortex uses more than double the amount of glucose compared to adults. This high

113 rate of glucose utilization is maintained from age 4 to 10. Childhood is a time of intense

114 learning and therefore coincides with the most metabolically expensive period[13]. The high

115 energy demand of a child's brain requires the use of the majority of hepatically generated

116 plasma glucose[14]. In addition, glucose supply needs to be particularly stable as impairments

117 are thought to occur at higher plasma glucose level (4.2 mmol/l)[15]. After this period, there

118 is a gradual decline in glucose metabolic rate, reaching adult values by age 16-18 years (see

119 for example[16]). This is followed by a plateau phase until middle age after when a significant

120 age-related decline in cerebral glucose metabolism can be observed (see for example[17]).

121 This age-specific metabolic pattern of glucose consumption has not been observed in other

122 species and it has been argued that this could be a driver or indeed a consequence of

123 human cognition[18].

124

125 Most children and young adults maintain circulating glucose within the normal range

126 throughout cycles of feeding and fasting and balanced alterations in secretions of regulatory

127 hormones. In contrast, older adults have a broader range over which circulating glucose is

128 maintained and in addition have attenuated counter regulatory responses. Circulating

4

129   insulin levels tend to be elevated with age (approx. 8% higher than in young adults) and are

130   indicative of reduced insulin sensitivity[19]. Reduced insulin sensitivity or insulin resistance is

131   a condition where individuals develop resistance to the cellular actions of insulin,

132   characterized by an impaired ability of insulin to inhibit glucose output from the liver and to

133   promote glucose uptake in fat and muscle. Both effects of insulin insensitivity on liver and

134   muscle tissue cause elevations in peripheral blood glucose levels. Changes in insulin action

135   have been observed at different stages of the development. Basal insulin secretion increase

136   during puberty, falling back to pre-pubertal levels in adulthood[20]. Yet, fasting glucose levels

137   remain constant, implying an increase in tissue resistance to insulin coinciding with

138   puberty[21]. The reason for the puberty-induced reduction of insulin sensitivity appears to be

139   growth-hormone related[22-24]. Growth hormone secretion reaches a peak at around puberty

140   and will begin to decrease by the age of 21 years[25]. It is commonly in middle age where

141   insulin resistance and poor glucose tolerance become a health issue. Given that the brain

142   uses glucose as a primary substrate for brain function, it is perhaps not surprising that

143   conditions that affect peripheral and central glucose regulation and utilization may also

144   affect cognitive functioning. Moreover, based on the evidence above there might be 'critical

145   periods' in which alterations in cerebral glucose supply might have more pronounced effects

146   on cognitive performance.

147

148   The consequences of fluctuations in central glucose availability have begun to be better

149   understood. Whereas initially it was thought that only glucose deprivation (i.e. under

150   hypoglycaemic conditions) can affect brain function it has become apparent that low-level

151   fluctuations in central availability can affect neural and consequently, cognitive

152   performance. In the next section we will review work into the phenomenon of cognitive

153   enhancement following a glucose load.

154

155   **Acute administration of a glucose load: prototypical experimental paradigm**

156   Over the last thirty years, a large body of literature has demonstrated beneficial effects of

157   acute glucose administration on cognition in various populations (for reviews see [26, 27]). The

158   general methodology used in these studies involves administration of an oral glucose load

159   (usual range between 25 and 50g of glucose) after a period of fasting (ranging from 2h to

5

160 overnight fast) followed by assessment of cognitive performance and measurement of

161 capillary blood glucose levels.

162

163 Using this experimental paradigm, beneficial effects have been observed across different

164 populations. For example, glucose administration has been shown to enhance cognitive

165 performance in adolescents[28], young adults[29-38], older adults[39, 40] and improvements have

166 been observed in subjects with mild or severe cognitive pathologies, including individuals

167 with Alzheimer's disease and Down's syndrome (see [26, 27] for reviews). In addition,

168 facilitation of cognitive performance induced by elevations in plasma glucose levels has also

169 been reported in patients with schizophrenia[41, 42]. It is important at this point to note that

170 these results do not reflect a negative effect of fasting on cognition and memory, as the

171 degree of fasting in which participants engaged was not exceptional and participants do not

172 reach blood glucose levels associated with hypoglycaemia. What these findings

173 demonstrated are the beneficial cognitive effects of raising blood glucose levels within

174 normal physiological limits.

175

176 Cognition is not a monolithic concept, but encompasses a range of mental processes which

177 occur when information is perceived, evaluated, stored, manipulated, retrieved or

178 otherwise processed. Important components of cognition are perception, attention,

179 vigilance, memory, executive function and language. These can be measures using different

180 task which in turn allow assessment of subcomponents. In terms of cognitive tasks affected,

181 benefits have been found to occur in a range of cognitive domains, including information

182 processing and attention[39, 43-46], working memory[29, 30, 35, 36, 47], executive function[48, 49]

183 problem solving[50] and long-term memory[29-31, 33-35, 51-53].

184

185 Trying to define the various aspects of cognition, which are most receptive to glucose-

186 induced enhancement, the clearest enhancement effects of increased glucose supply have

187 been observed for verbal declarative long-term memory over a variety of conditions and

188 paradigms (for review see[54]). As different aspects of cognition pertain to different neural

189 structures and network, this allows speculation about the areas of the brain that might be

190 particularly susceptible to glycaemic fluctuations. The robust effects on long-term memory,

191 suggest that glucose facilitation may be particularly pronounced in tasks that pertain to the

6

192   hippocampal formation[29]. The level of task demand is a further moderating factor for

193   cognitive enhancement by increased glucose availability. Indeed, in younger participants,

194   glucose-related improvement of cognition appears to be related to the difficulty of the

195   cognitive tasks. Tasks which are more cognitively demanding appear to be more sensitive to

196   the effect of glucose loading[30, 36, 55]. In addition, 'depletion' of episodic memory capacity

197   and/or glucose resources in the brain due to performing a concomitant cognitive task might

198   be crucial to the demonstration of a glucose facilitation effect. The reason for this is likely to

199   be that younger individuals already working at optimal physiological and cognitive efficiency

200   (and therefore functioning at or near a ceiling level of performance), whereas older

201   participants and clinical patients are unable to achieve optimal performance due to age- or

202   illness-related degenerative changes.

203

204   Indeed, while both young and older adults show cognitive improvement after the oral

205   administration of glucose, the effects appear to be more profound in older individuals.

206   Cognitive decline over the aging process has been well documented[56-58]. Traditionally,

207   cognitive impairments are assumed to reflect deficits caused by damage of brain areas or

208   systems in which cognitive processing in normal subjects occurs. However, more recently

209   there has been a focus shift on specific physiologic and metabolic impairments that appear

210   to contribute to the cognitive decline observed in ageing. Older adults have a broader range

211   over which circulating glucose is maintained and in addition have attenuated counter

212   regulatory responses. These suboptimal metabolic and cognitive conditions are likely to

213   make older individuals more susceptible to glucose facilitation of cognitive performance.

214

215   The energy cost for effortful, controlled or executive processes appears to be significantly

216   higher than that for automatic or reflexive processes[59]. Effortful, controlled or executive

217   processes are processes that are reliant on the central executive, in which thoughts,

218   behaviours and actions are coordinated to allow goal directed and purposeful behaviour[60],

219   while automatic and reflexive behaviours are evolutionarily predisposed or learned

220   behaviours elicited by environmental stimuli. Indeed, lowered peripheral glucose levels

221   following performance of a cognitively demanding task have been reported[55, 61]. This fall in

222   plasma glucose could reflect a more efficient transfer of glucose to the brain which in turn

223   results in increased provision centrally. One should be cautious when making assumptions

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224   about peripheral blood glucose levels and their putative effects on the brain, as other

225   studies have failed to demonstrate such findings[62, 63]. Nevertheless, the evidence suggests

226   that cognitively demanding tasks and in particular those relying on executive functions are

227   also sensitive to changes in glucose (see for example[59, 64]) Administration of a glucose drink

228   would consequently provide the brain with sufficient metabolic resources for extensive

229   cognitive processing and support the brain areas under greatest cognitive load, and thus

230   lead to improved performance.

231

232   Apart from task difficulty and cognitive domain, the amount of glucose administered is also

233   an important factor. As with many substances affecting cognitive performance, glucose

234   displays an inverted U-shaped dose-response curve, and its effect is time dependent[3]). For

235   older adults 25g of glucose appear to be the optimal dose, with performance deterioration

236   observed after administration of 75g of glucose[65]. For young adults 25g also seems to most

237   reliably facilitate cognitive performance, however, there is evidence suggesting that the

238   optimal dose or shape of the dose-response curve may be dependent on inter-individual

239   difference in glucose metabolism, and the cognitive domain being assessed[33]. Of note, the

240   cognitive enhancing effects of pharmaceutical substances such as stimulants

241   (methylphenidate, modafinil) and acetylcholinesterase inhibitor (dementia drugs) in healthy

242   individuals are generally moderate or small (as estimated by Cohen's d effect size) according

243   to systematic reviews (see for example[66, 67]). The effects of glucose administration are

244   comparable with those from pharmaceutical interventions, with effect sizes for glucose

245   effects range from 0.34 to 4.26, with typical values of 1.02, 0.81 and 1.07 for heavily loaded

246   working memory and verbal episodic recognition and recall respectively[68].

247

248   **Glucose facilitation of cognitive performance: putative underlying mechanisms**

249   The precise mechanisms by which increased peripheral and/or central glucose availability

250   affects cognitive processes are still unclear. There are two broad theoretical approaches:

251   energetic demand models and domain specific models. Energetic demand models, have

252   their basis in the observation that the amount of mental effort involved in cognitive

253   processing is an important determinant of a task's susceptibility to glucose enhancement.

254   Domain specific theories, on the other hand stipulate that certain areas of the brain are

255   more susceptible to changes in glucose availability. However, as will become clear these

8

256 different approaches are by no means mutually exclusive, their relative explanatory value

257 depending on cognitive task and brain structure.

258 Glucose metabolism varies throughout tissue/cell types of the brain, with a clearly

259 established correlation between increased energy metabolism and increased neuronal

260 activity and energy metabolism[69].Both the rate of blood to brain glucose transport[70] and

261 glucose metabolism[71] are stimulated in different areas in the brain during cognitive tasks

262 relevant to that area. There is evidence that performing cognitively demanding tasks

263 increases total brain consumption by as much as 12%[72].

264

265 As described, glucose exerts quite robust effects on long-term memory tasks. The

266 hippocampus is the brain region most strongly implicated in long-term memory

267 performance[73]. Microdialysis measurements of brain glucose have shown a large decrease

268 in hippocampal extra cellular fluid (ECF; 32 $\pm$ 2%) in rats tested for spontaneous alternation

269 on a four-arm maze (a difficult memory task), while a smaller decrease (11 $\pm$ 2%) was seen

270 in rats tested on a simpler three arm- maze, suggesting that the changes observed in ECF

271 glucose are related to task difficulty. The fall in ECF can be prevented by administration of

272 glucose, which in turn leads to enhanced memory performance[74]. There is some evidence

273 that the concentration of extracellular glucose in the brain after its transfer across the

274 blood-brain barrier from plasma glucose varies with brain region from 1.3 mmol/l in the

275 hippocampus to 0.3-0.5 mmol/l in the striatum (for review, see[75]). These findings suggest

276 that the hippocampal area is particularly sensitive to energy fluctuations. However, the

277 hippocampus has relatively greater glycogen stores compared to other areas suggesting that

278 it has evolved some protection against temporary deficits (13 mmol/l compared to 5-6

279 mmol/l in the cerebral cortex[76].

280

281 Research also shows that difficult tasks are more likely to be susceptible to glycaemic

282 interventions. Difficult tasks include those involving executive functions pertaining to frontal

283 brain regions: inhibition/self-control, working memory and mental flexibility[77, 78]. Evidence

284 suggested that tasks that demand such cognitive control and attentional resources appear

285 to be more energy demanding[59]. Consequently, another area of the brain which appears to

286 be particularly sensitive to energy fluctuations is the frontal cortex. The cerebral cortex, and

287 in particular the prefrontal cortex, represents the neural basis of higher cognitive functions

9

288   e.g[79, 80]. Aspects of higher-level cognition were probably one of the last cognitive abilities to

289   develop ontogenetically. Based on the "last-in, first-out rule", cognitive abilities that

290   developed last ontogenetically are likely the first to become impaired when cognitive and/or

291   physiological resources are compromised. Consequently, optimal performance on task

292   pertaining to function of the pre-frontal cortex might require more energetic fuel than

293   others.

294

295   From an evolutionary perspective, energy mobilization is of particular importance in times

296   of stress in order to prepare the body for the "fight or flight" response. Exposure to threats

297   or stressors results in activation of two major endocrine systems, the hypothalamic-anterior

298   pituitary-adrenocortical axis (HPA) and the sympatho-adrenomedullary axis (SAM axis). A

299   major physiological role of activation of both endocrine systems is considered to be a

300   temporary increase in energy production and more specifically provision of additional

301   metabolic fuel through increase in glucose availability[81]. Liberation of additional metabolic

302   resources allow the organism to adapt rapidly to such environmental challenges.

303

304   From a memory perspective such endogenous processes could act as relevance moderators

305   of the "print-now" signal by regulating encoding and synaptic plasticity[82]. That is to say

306   they could moderate memory strength and contribute to memory formation by selectively

307   promoting the storage of significant events and not trivial ones[83, 84]. In terms of its

308   influence on prefrontal cortex function, these processes could moderate energy supply,

309   allowing allocation of optimal resources to functions relevant to survival. Administration of

310   a glucose load might by-pass the above mentioned endocrine activation and the

311   concomitant increased peripheral and/or central glucose availability could lead to optimal

312   energy supply.

313

314   Glucose has other important mechanisms of action in the central nervous system, including

315   interactions with various neurotransmitter systems (e.g. acetylcholine, dopamine, opiates).

316   There is evidence suggesting that the cognitive facilitation observed after glucose loading is

317   due to an increase in enhancement of acetylcholine synthesis and/or release (see[26] for

318   review). However, effects on neurotransmitter systems and energy supply theories are not

319   mutually exclusive. For example, Peters et al.[85] proposed a model for brain energy supply

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320   controlled by high-affinity and low-affinity ATP sensitive potassium channels in neocortical

321   neurons. According to the model, high-affinity ATP sensitive potassium channels are located

322   on excitatory neurons, whereas those with low-affinity are located on inhibitory neurons.

323   Occupancy of these channels changes depending on ATP levels whereby low (but not

324   critically low) ATP concentration would lead to excitatory glutamatergic neuronal activity,

325   whereas at high ATP levels a shift towards predominately inhibitory GABA-ergic neuronal

326   activity occurs[85]. Moreover, Sandberg et al[82] described a model of an autoassociative

327   network with plasticity modulation that produced an inverted U-shaped curve to overall

328   plasticity similar to the one commonly observed in arousal-performance or glucose dose-

329   response plots. Additional energy availability could result in optimal neuronal activation as

330   defined by optimal balance of inhibitory and excitatory activity which in turn results in peak

331   cognitive performance.

332

333   In addition, elevated insulin in response to hyperglycaemia rather than glucose levels *per se*

334   may moderate memory performance (see[86] for review). Originally, insulin was considered

335   only as a peripheral hormone, unable to cross the blood-brain barrier (BBB) and to affect

336   the central nervous system (CNS). However, there is now increasing evidence that neuronal

337   glucose metabolism is antagonistically controlled by insulin and cortisol (see[87, 88] for

338   reviews). Insulin present in adult CNS is primarily derived from pancreatic β-cells and is

339   transported by CSF into the brain. It is also partially formed in pyramidal neurons, such as

340   those in the hippocampus, prefrontal cortex, entorhinal cortex and the olfactory bulb, but

341   not in glial cells[89]. The suggestion that glucose administration and/or impairments in

342   glucoregulatory mechanisms exert the most profound effects on medial temporal regions is

343   supported by functional characteristics associated with these areas such as high density of

344   insulin receptors in the hippocampus (e.g. [90, 91]) which are known to promote cellular

345   glucose uptake (e.g. see [26, 92]). Insulin-sensitive glucose transporters such as GLUT4 (which

346   mediate passive diffusion of glucose through the blood brain barrier) are also enriched in

347   the hippocampus (though the highest concentration is in the cerebellum, see[93]. Given the

348   established role of the hippocampus in memory, elevated insulin in response to

349   hyperglycaemia may boost glucose utilization in the hippocampus and result in improved

350   performance[94]. Indeed, at the molecular level, insulin and/or insulin receptors seem to

351   contribute to the regulation of learning and memory via the activation of specific signalling

11

352   pathways, one of which is shown to be associated with the formation of long-term memory

353   (for a more detailed account see [95, 96].

354

355   Lastly, glucose might also act via peripheral physiological mechanisms, which in turn

356   facilitate central mechanisms involved in cognition. It has been suggested that important

357   players in this peripheral route are the liver and the vagus nerve. Messier and White [97, 98]

358   suggested that changes in cell membrane transport in the liver following administration of

359   high doses of glucose and fructose (> 1000mg/kg) are detected by the coeliac ganglion, then

360   transformed into neural signals and finally carried via the vagus nerve to the brain. In

361   accordance with this suggestion, coeliac ganglion lesions (which block most of the efferents

362   of the liver) have been shown to abolish the mnemonic effect of glucose[98]. To date there is

363   no concrete information available concerning how this proposed neural signal from the liver

364   might influence cognitive performance when it reaches the brain. However, the nucleus of

365   the solitary tract (NST) in the brain stem is the main relay station for afferent vagal nerve

366   fibers. This nucleus has widespread projections to numerous areas in the cerebral cortex,

367   including the hippocampus and the prefrontal cortex and stimulation of the vagus nerve

368   induces changes in the electrophysiological and metabolic profile of these brain

369   structures[99]. The research is not yet conclusive, but suggests that the underlying

370   mechanism is multifarious. The most likely scenario is that glucose provides additional

371   metabolic fuel under high demand conditions and that certain areas of the brain are more

372   susceptible to limitations in fuel supply, or are evolutionarily programmed to react to an

373   endogenous rise in plasma glucose levels.

374

375   **Glycaemic regulation and cognition**

376   The investigations into the effects of administration of a glucose load have been important

377   in elucidating the potential underlying mechanisms. Acute administration of a glucose load

378   has been shown to benefit cognitive performance. This can be advantageous in conditions

379   where there is a need for fast 'fuel refill', for example in situations of stress combined with

380   physical performance (see e.g.[100]). However, over longer time periods, elevated blood

381   glucose levels act as an allostatic load to biological system and can accelerate disease

382   processes. Due to the complex relationship between glucose administration, glucose

383   metabolism and cognition, inducement of repeated hyperglycaemic conditions would

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384   eventually result in performance decrements as it affects glycaemic regulation, i.e. the

385   ability of the body to effectively regulate blood glucose levels and to remove glucose from

386   the blood. Blood glucose levels of healthy individuals respond to glucose ingestion by rising

387   for roughly half an hour and then returning to near baseline measures within 2 hours,

388   whereas in individuals with poor glucose tolerance, blood glucose levels commonly peak

389   quickly and then fall more slowly.

390

391   Impairments in glucose and insulin regulation lead to increases in plasma glucose levels, but

392   decreased glucose utilization due to insulin resistance. Given the dependence of the brain

393   on glucose for optimal functioning and the evidence showing that acute glucose

394   administration can influence cognitive function it is not surprising that impaired glycaemic

395   control may contribute to cognitive impairments (see[101] for a review of the literature).

396   Consequently, in addition to food intake, glycaemic control is another important factor

397   when considering cognition across the life-span. Conditions in which glycaemic regulation is

398   severely compromised are diabetes type 1 and type 2, impaired glucose tolerance (IGT), and

399   impaired fasting glucose (IFG). Cognitive impairments were indeed one of the earliest

400   recognized neurological complications associated with diabetes[102]. To date, numerous

401   studies have compared cognitive functioning in diabetic patients with non-diabetic

402   controls[103]. Although these studies differed widely with respect to patient characteristics

403   (age, duration and type of diabetes) and cognitive tests used, the majority of these studies

404   demonstrated cognitive impairments in this population which included decreased

405   performance on various attention and memory tasks[101, 104-107]. Risk factors associated with

406   cognitive complications in diabetes appear to be i) degree of metabolic control[108] and ii)

407   repeated episodes of hypoglycaemia[109]. It is therefore not surprising that in children

408   diagnosed with Type 1 diabetes before age 10 years, cognitive complications are generally

409   only observed if they have a history of hypoglycaemic seizures[110]. It is evident from the

410   literature that Type 2 diabetes is the metabolic condition associated with an increased risk

411   of cognitive dysfunction[111-113].

412

413   However, there is now increasing evidence of a relationship between glycaemic control and

414   cognitive functions in healthy, non-diabetic populations (see [101, 105] for reviews). As

415   mentioned earlier, impairments in glucose tolerance become a larger issue in middle age

13

416 and consequently it is likely that the negative cognitive impact of abnormalities in glucose
417 tolerance increases with age. Cognitive decline over the aging process has been well
418 documented and it has been suggested that normal aging may represent a condition in
419 which there is greater vulnerability to disrupted glucose regulation (see for example[58]).
420 Indeed, evidence to support this hypothesis is provided by the finding that memory
421 performance in elderly participants with poor glucose regulation is impaired relative to
422 elderly participants with good glucose regulation[114-116]. Moreover, age-related changes in
423 glucose metabolism have been identified as a risk factor for Alzheimer's disease [26, 86, 117].
424 Consistent with this notion is the finding that hyperglycaemia (induced through oral and
425 intravenous glucose administration) can facilitate memory performance in Alzheimer's
426 patients, at least in the early stages of the disease[118]. Interestingly, alterations in blood
427 glucose regulation seem to depend on the severity of the disease process. More specifically,
428 high insulin levels are observable at the very early ('very mild') stages and decline as
429 dementia progresses. Moreover, memory facilitation can be achieved through glucose
430 administration in the early stages and the degree of facilitation decreases at more advanced
431 stages of the disease[94]. Indeed, as abnormalities in brain insulin resistance and deficiency
432 have been observed in Alzheimer's disease, and the fact that molecular and biochemical
433 hallmarks of Alzheimer's disease, such as neuronal loss, synaptic disconnection, tau
434 hyperphosphorylation, and amyloid-beta accumulation overlap with Type 1 and Type 2
435 diabetes, the term "Type 3 diabetes" has been suggested to account for the underlying
436 abnormalities associated with AD-type neurodegeneration[119].

437

438 However, and perhaps more worryingly, performance decrements due to poor glucose
439 regulation have been reported in younger individuals (see [101, 105] for reviews). For example,
440 recent studies have shown that even in a healthy young student population those with
441 better glucose regulation (those who had the smallest blood glucose rise following glucose
442 ingestion) perform better on tests of memory[35, 49, 105, 120-122], vigilance[49, 120], planning[120]
443 and dichotic listening[123] compared to those with poorer glucose regulation. In addition,
444 glucose administration preferentially improved performance in those with poorer glucose
445 regulation and the effects are less likely to be observed in good glucose regulators in both
446 old and young populations[26]. This would suggest that glucose control or tolerance is
447 associated with cognition throughout the lifespan. Overall there appears to be some

14

448   evidence that glucoregulation may exert direct effects on cognitive function in that those

449   with poor glucoregulation may demonstrate mild cognitive deficit compared with good

450   glucoregulation. However, research in young adults is limited, furthermore the

451   methodologies for determining glucoregulatory control have been varied. Only a few studies

452   have used a standardized oral glucose tolerance test (OGTT) for the evaluation of glucose

453   tolerance in healthy young adults (for example [35, 124]). The OGTT involves administration of

454   a 75g glucose load after a minimum eight hour fast and is the gold standard test for the

455   diagnosis of diabetes mellitus (WHO, 1999). Moreover, the majority of studies have only

456   assessed one specific measurement of glucose tolerance. Several glucoregulatory indices

457   have been previously evaluated for their relationship with cognitive performance in younger

458   and older participants. These include: fasting levels, peak glucose levels, recovery and

459   evoked glucose to baseline levels and incremental area under the curve (AUC) (see[35]). At a

460   younger age, the deficits associated with poor glucoregulation may be minimal and hard to

461   detect therefore it is important to identify the most sensitive marker. A study in our

462   laboratory found AUC, which takes baseline blood glucose levels into account (AUC with

463   respect to ground; see[125]

464

465   for calculations), to be the best predictor of cognitive performance, whereas the most

466   commonly used incremental AUC did not show a strong association[35]. This suggests that

467   overall circulating glucose levels may be an important factor in the assessment of

468   glucoregulation in sub-clinical; populations with normal glucose tolerance as defined by the

469   World Health Organisation (WHO). Indeed, a recent study identified fasting blood glucose

470   levels as a predictor for cognitive performance[126]. Young adults who were obese but

471   otherwise healthy had higher fasting glucose levels compared with normal weight

472   participants. In addition, higher glucose levels were associated with poorer cognitive

473   performance on tests of inhibitory control, especially among individuals with pre-diabetic

474   levels. Consequently, subclinical elevations in blood glucose may contribute to cognitive

475   impairments before the development of clinically defined disease states.

476

477

478   **The postprandial glycaemic response and cognition**

15

479　When considering the nature of glucose availability, the rate at which food increases and

480　maintains blood glucose, i.e. 'the Glycaemic Index' (GI) appears to be an important

481　modulating factor. Shortly after intake of a high GI food there is a relatively rapid rise in

482　blood glucose levels followed by a corresponding rapid decrease, whereas after the intake

483　of a low GI food there is a relatively smaller rise in blood glucose followed by more stable

484　blood glucose concentration. GI solely provides a measure of carbohydrate quality[127],

485　whereas glycaemic load (GL) takes into account the amount of carbohydrates consumed and

486　is calculated by multiplying the amount of available carbohydrate in a food item by the GI of

487　the food and dividing this by 100[128].

488

489　Although the effect of glucose administration has been extensively studied in an acute,

490　short-term context, much remains to be done in order to establish the cognitive effects

491　associated with foods of low or high GI and GL. When looking at effects across the life-span,

492　children may be particularly sensitive to glycaemic effects on brain activity and associated

493　cognitive outcomes. As outlined previously, the reason for the greater susceptibility is likely

494　to be due to greater energetic needs during this period compared to adults (see for

495　example[16]) Moreover, it has been suggested that in younger children, the overnight fast

496　induces greater the metabolic stress, as the higher the ratio of brain to liver weight and the

497　greater the metabolic rate per unit of brain weight, the greater the demand on glycogen

498　stores[129] Most studies examining the effects of GI on cognition have focused on the effect

499　of breakfast on children's cognitive performance. It has been shown that children at risk for

500　malnourishment have improved cognition and learning at school if provided with breakfast

501　(see[130] for a review of the literature). Moreover, in developed countries it has been found

502　that skipping breakfast can result in impaired cognitive performance[130, 131]. This suggests

503　that increased plasma glucose availability due to breakfast consumption leads to better

504　cognitive performance. Investigating the optimal rate of glucose supply following breakfast

505　consumption[132], compared a low GI breakfast with a high GI breakfast and found that when

506　children consumed the low GI food they remembered significantly more than when they ate

507　the high GI breakfast. Ingwersen et al[133] compared the cognitive effects of a low GI

508　breakfast and a high GI breakfast across the morning and found that performance on

509　attention tasks was poorer 130 minutes after the high GI breakfast compared to the low GI

510　breakfast. Furthermore, the low GI breakfast prevented a decline in memory performance.

16

511   Overall, the results of studies assessing GI in children suggest that a lower postprandial

512   glycaemic response may be protective against a decline in memory and attention

513   throughout the morning[132-139]. However, the evidence is far from conclusive[140, 141] and few

514   studies have actually profiled the glycaemic response in children[142].

515

516   From a metabolic perspective, adolescence might also be a time where greater susceptibility

517   to glycaemic variations is observed due to the specific metabolic conditions observed during

518   that time of development.   However, few studies have looked at the effects of GI in

519   adolescent populations and the results are somewhat contradictive. Wesnes et al[134] found

520   that a low GI breakfast resulted in better memory performance and attention, but the age

521   range used in this study was quite large (6-16 years). Other studies found performance

522   benefits following a high GI intervention when assessing memory performance[137, 143]

523   whereas   a   low   GI   intervention   proved   to   be   beneficial   for   measures   of

524   attention/information processing[137]. Cooper et al. (2012) found no difference between

525   high GI and low GI on reaction times, but better performance on an executive function task

526   following low GI[138].

527

528   In adult populations, the outcome of investigating the effects of GI has also been somewhat

529   inconsistent. Some show beneficial effects on cognitive performance of low-GI foods[135, 144,

530   145] whereas others show no such effects [146, 147]. Benton et al[136] compared three breakfasts

531   varying in GL from 2·5 to 17·86 and found that the higher GL foods led to poorer memory

532   performance. Lamport et al[148] investigated the effects of low GI and high GI evening meals

533   followed by a high GI standard breakfast on subsequent cognitive performance. Although no

534   significant differences between evening meals on cognitive performance were observed, the

535   high GI evening meal was associated with better memory performance the following

536   morning after breakfast had been consumed.

537

538   To date only a few studies have been carried out into the effect of low GI and GL foods on

539   glycaemic control and cognition in older adults, or populations with pre-existing metabolic

540   and/or cognitive impairments. Kaplan et al. (33) found no differences between meals of dif-

541   ferent GI in performance in elderly adults. Nilsson, Radeborg and Bjork[144] showed that in a

17

542 sample ranging from 49–70 years, performance was better in the late postprandial period
543 after consumption of a low-GI compared to a high-GI breakfast. In adults with type 2
544 diabetes consuming a low-GI carbohydrate meal, relative to a high-GI carbohydrate meal,
545 has been shown to result in better cognitive performance in the postprandial period[149].
546 However, two other studies by Lamport et al.[148, 150] did not find any benefits following
547 consumption of a low glycaemic load breakfast. All of these studies investigated the acute
548 effects of postprandial glycaemic manipulation and it may be the case that for these
549 populations cognitive effects will only be evident with chronic improvements in glycaemic
550 control. Indeed, dietary interventions (combined with exercise interventions) have been
551 shown to result in improved cognitive performance in adults with impaired glucose control
552 when they were implemented for 12 months[151].

554 Overall, it appears that a quick rise in blood glucose levels has some short-term benefits,
555 most notably on memory performance; whereas over longer periods of time (i.e.
556 throughout the morning) a more stable blood glucose profile seems to be more beneficial.
557 In normoglycaemic samples, effects of low GI and/or low GL foods were usually observed in
558 the late postprandial period (75-222 min) where they seem to prevent a decline in attention
559 and memory[132, 133, 135]. In populations with abnormalities in glucose regulation, benefits of
560 low GI foods have been reported in particular following longer-term intervention.

562 **Conclusion**

563 Based on the evidence it is clear that avoiding peaks and troughs in glucose availability is key
564 to optimal cognitive performance. Administration of a glucose load does not represent a
565 viable strategy over any prolonged timeframe since consistently elevated blood glucose
566 leads to insulin resistance. Habitual diets that are rich in refined/simple carbohydrates also
567 lead to high blood glucose. As described earlier, following ingestion of low GI and/or GL food
568 there is a relatively smaller rise in blood glucose followed by more stable blood glucose
569 concentration. Although the evidence to date is promising, there is an urgent need for
570 hypothesis driven, randomised controlled trials that evaluate the role of different glycaemic
571 manipulations on cognition. A relatively recent review into the effects of carbohydrates on
572 cognition in older individuals identified only one study that fulfilled these criteria[152]. The
573 study that was included investigated the acute effects of a glucose drink[153], whereas

18

574   studies investigating more complex carbohydrates were not. Future research comparing the

575   effects of different types of carbohydrates, with differing glycaemic profiles are clearly

576   needed. What limits our ability to draw strong conclusions from the findings of previous

577   studies is the fact that they often differ widely with respect to subject characteristics and

578   cognitive tests used. Future research needs to carefully consider conceptual and

579   methodological factors including potential inter-individual differences, adequate selection

580   of tests and control of extraneous (confounding) variables (for a detailed account of

581   methodological issues see [154]).

582

583   Moreover, when assessing food items in terms of health benefits and potential dangers, we

584   need to remember that in a habitual diet (as opposed to some of the experimental

585   interventions described earlier), carbohydrates are rarely ingested in isolation. Co-ingestion

586   of other nutrients and nutritional compounds alters the rate of carbohydrate degradation

587   during digestion and consequently affect regulation of postprandial blood glucose and

588   insulin levels. For example, a lowering of glycaemic response has been found when purified

589   extracts of fibre are added to a test food in sufficient quantity [155-158]. Moreover, high fibre

590   diets have been shown to decrease postprandial blood glucose levels[159], improve glycaemic

591   control in diabetic populations and decrease the risk of Type 2 Diabetes[160, 161]. Similarly,

592   dietary proteins have been found to have positive effects on insulin production in

593   populations with normal glucose metabolisms as well as type 2 diabetics[162-164]. Another

594   factor that needs to be considered is the amount and the type of fat consumed. Evidence

595   suggests that the risk of impaired glucose regulation and Type 2 diabetes is associated with

596   a high *trans* fatty acid intake and a low poly-unsaturated to saturated fat intake ratio[165].

597   There are reports stating that saturated and *trans* fatty acids increase insulin resistance,

598   whereas poly-unsaturated fats decrease resistance and offer protection against disease

599   (see[166]). Consequently, diets high in saturated fats or trans fats should be avoided as they

600   are likely to interfere with glucose tolerance and insulin sensitivity.

601

602   In conclusion, a habitual diet that secures optimal glucose delivery to the brain in the fed

603   and fasting states should be most advantageous for the maintenance of cognitive function.

604   This can be achieved by adhering to a low saturated fat and low glycaemic load diet–

605   especially when combined with sufficient physical exercise, which has also been shown to

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606   significantly reduce the risk of developing impairments in glucose metabolism (see for

607   example[167]). This combination of diet and exercise has been demonstrated to have

608   cognitive and metabolic benefits (improved glucose and insulin metabolism) in adults with

609   impaired glucose tolerance[151]. Dietary lifestyle changes can have a positive impact

610   throughout the lifespan and appear to not only reduce the risk of acquiring cognitive

611   impairments, but can also attenuate existing impairments. For example, a recent study

612   showed that a 4-week low-saturated fat/low-glycaemic index diet resulted in improved

613   memory performance and insulin metabolism in adults with amnestic mild cognitive

614   impairment[168].

615

616   The rise in obesity, diabetes and metabolic syndrome in recent years highlights the need for

617   targeted dietary and lifestyle strategies to promote healthy lifestyle and brain function

618   across the lifespan and for future generations. The data indicate that modifiable lifestyle

619   factors and most notably dietary changes may contribute significantly to optimal cognition

620   across the lifespan. Consequently, the therapeutic effects of longer-term dietary

621   intervention may be a promising avenue of exploration. Lifestyle changes are difficult to

622   execute and to maintain, but present an exciting potential for optimizing cognitive

623   performance across the lifespan.

624

625

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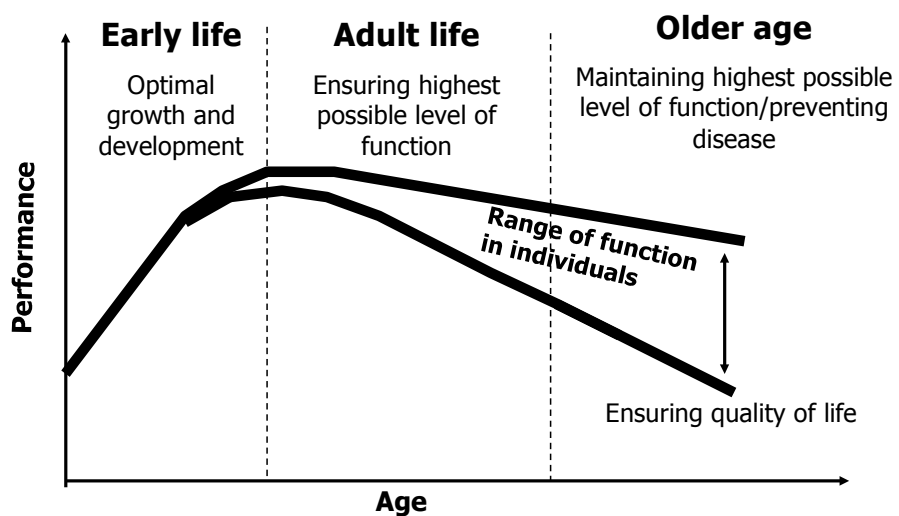872   diabetes on cognitive performance. Diabetes care. 2005;28(3):726-35.

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Figure 1: Nutrition and cognition: potential for optimizing cognitive performance across the lifespan