Caffeine and Memory

A digest of reports of research into the direct and indirect effects of caffeine on cognitive performance.

BY DR FIONA MCPHERSON

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Summary

Caffeine generally improves alertness and reaction time, but evidence is inconclusive for its effect on higher memory and reasoning processes. It is possible that caffeine may in fact impede memory, where the information is complex or ambiguous.

It also seems that caffeine has different effects depending on the individual, with age, gender, personality traits, and history of caffeine consumption, all important factors.

Caffeine can be helpful in ameliorating the effects of time of day and sleep deprivation on cognitive performance. In normal circumstances (i.e., not prolonged sleep deprivation, or extreme stress), caffeine seems to be more helpful to older adults, in helping them overcome time-of-day effects.

Recent research has demonstrated that caffeine affects blood flow in the brain. It is not yet clear what the implications of this may be.

Caffeine has been implicated in raising blood pressure. High blood pressure is undoubtedly a risk factor for cognitive decline and dementia for those over 60. However, recent studies suggest that, while it is clear that coffee raises blood pressure, it is not clear that caffeine is the culprit.

Brewed coffee raises homocysteine levels. High homocysteine levels in older adults increase the risk of cognitive decline and dementia. Recent research suggests however that caffeine is not the sole ingredient in coffee responsible for the homocysteine-raising effect.

Evidence for the effect of caffeine on glucose regulation is inconclusive as yet, but there is some suggestion that caffeine may be a risk factor for impaired glucose tolerance. Impaired glucose tolerance is a risk factor for cardiovascular disease (and thus, by implication, cognitive decline, since research now indicates that "what is good for the heart is good for the brain"). More direct evidence also suggests that impaired glucose tolerance in older adults is associated with memory problems.

While people clearly build up a tolerance to some of the effects of caffeine, it is not yet clear what the long-term effects of regular caffeine use are. Nor can we say, as yet, what factors are important in determining those long-term effects, although we can speculate that gender, metabolic factors, cardiovascular health, alcohol and tobacco use are all possible influences.

Animal studies support the value of regular caffeine consumption in reducing the risk of developing Alzheimer's disease, but human studies have been less consistent.

Conclusion: Clearly, caffeine has both good and bad effects, both of which may impact on cognitive performance. Moreover, the main vehicle for caffeine — coffee — contains active ingredients other than caffeine which may, directly or indirectly, impact on cognitive performance. Caffeine does appear to be of greater potential significance to older adults. Overall, the evidence suggests that, while caffeine may help older adults in the later part of the day, those with hypertension, diabetes, impaired glucose tolerance, or high homocysteine levels, would be wiser to avoid coffee, even if decaffeinated. In general, while caffeine may help you overcome factors that

lower your cognitive performance, it does not seem that caffeine has any significant direct effect on memory, although it may well help you pay attention.

Caffeine and cognitive performance

Summary

A study of older adults found higher lifetime consumption of caffeinated coffee was associated with better performance on several cognitive tests — for women, but not men. However, another study found that boys were more affected by caffeine than girls.

Inconsistent results may be explained by research indicating that caffeine has different effects depending on the individual's attitude to work. Perhaps apparent differences in gender effects reflect other individual differences we haven't investigated yet.

One significant factor is likely to be an individual's history of caffeine consumption. Some research suggests that caffeine only appears to improve attention because it counters the effects of caffeine withdrawal.

Another factor may be age, with caffeine of more benefit to older adults.

Some studies have found that caffeine led to increased alertness and improved performance on several simple cognitive tasks.

However, while caffeine undoubtedly improves reaction time, facilitating those cognitive tasks which are measured in terms of speed, it is not clear that caffeine improves tasks that involve more complex cognitive processes.

Conclusion: Caffeine may improve alertness and reaction time, but evidence is inconclusive for its effect on higher memory and reasoning processes, and positive effects may depend on individual characteristics, such as age, gender, personal characteristics, and history of caffeine consumption.

News reports

Coffee consumption unrelated to alertness

A recent study indicates that the alertness benefits of caffeine may simply reflect the reversal of the fatiguing effects of caffeine withdrawal.

A study involving 379 individuals who abstained from caffeine for 16 hours has revealed little variance in levels of alertness after receiving caffeine. Those who were medium/high caffeine consumers reported a decrease in alertness and an increase in headache if given the placebo, neither of which were reported by those who received caffeine. However, their post-caffeine levels of alertness were no higher than the non/low consumers who received a placebo, suggesting caffeine only brings coffee drinkers back up to 'normal'. In other words, the stimulatory effect of caffeine appears to be an illusion generated by the reversal of the fatiguing effects of acute caffeine withdrawal.

Rogers, P. J., Hohoff C., Heatherley S. V., Mullings E. L., Maxfield P. J., Evershed R. P., et al. (2010). Association of the Anxiogenic and Alerting Effects of Caffeine with ADORA2A and ADORA1 Polymorphisms and Habitual Level of Caffeine Consumption. Neuropsychopharmacology.

www.physorg.com/news194712919.html

Chocolate, wine and tea improve brain performance

A study of over 2000 older Norwegians (aged 70-74) has found that those who consumed chocolate, wine, or tea had significantly better cognitive performance and lower risk of poor cognitive performance than those who did not. Those who consumed all 3 studied items had the best performance and the lowest risks for poor test performance. The associations between intake of these foodstuffs and cognition were dose dependent, with maximum effect at intakes of around 10 grams a day for chocolate and around 75–100 ml a day for wine, but approximately linear for tea. The effect was most pronounced for wine and modestly weaker for chocolate intake. The finding is consistent with research indicating that those who consume lots of flavonoids have a lower incidence of dementia.

Nurk, E., Refsum H., Drevon C. A., Tell G. S., Nygaard H. A., Engedal K., et al. (2009). Intake of flavonoid-rich wine, tea, and chocolate by elderly men and women is associated with better cognitive test performance. The Journal of Nutrition. 139(1), 120 - 127.

http://www.physorg.com/news149185135.html

Effects of breakfast and caffeine on cognitive performance, mood and cardiovascular functioning

Two experiments examined the effects of a cooked breakfast, a cereal/toast breakfast, and caffeine (4 mg/kg). Breakfast improved performance on free recall and recognition memory tasks, but had no effect on a semantic memory task and lowered performance on a logical reasoning task. Caffeine improved performance on all of these cognitive tasks.

Smith, A., Kendrick, A., Maben, A. & Salmon, J. 1994. Effects of breakfast and caffeine on cognitive performance, mood and cardiovascular functioning. *Appetite, 22*, 39-55.

Caffeine's effect on cognitive performance

Some 9000 British adults were surveyed to investigate the relationship between habitual coffee and tea consumption and cognitive performance, measured by tests of simple reaction time, choice reaction time, incidental verbal memory, and visuo-spatial reasoning.

For all tests, higher levels of coffee consumption were association with higher performance. Similar but weaker associations were found for tea consumption, but these were significant only for simple reaction time and visuo-spatial reasoning. Caffeine appeared to benefit older people more than younger people.

Jarvis, M.J. 1993. Does caffeine intake enhance absolute levels of cognitive performance? *Psychopharmacology (Berl), 110*, 45-52.

Working memory impairment with too much caffeine

The effects of caffeine on mid-morning cognitive performance were investigated in 32 male subjects. Participants were given drinks containing either no caffeine, 125 mg caffeine, or 250 mg caffeine. They were then tested on three tasks: 1) free recall of word lists, 2) a response time task, and 3) a numerical Stroop task.

There were no significant effects of caffeine on the recall task or in response times, but those who were given the higher caffeine dose were seriously impaired on the Stroop test, making particularly slow responses.

The researchers suggest that caffeine may have a deleterious effect on the rapid processing of ambiguous or confusing stimuli.

Foreman, N., Barraclough, S., Moore, C., Mehta, A. & Madon, M. 1989. High doses of caffeine impair performance of a numerical version of the Stroop task in men. *Pharmacology, Biochemistry & Behavior, 32*, 399-403.

Individual differences in caffeine effects

Caffeine's effect varies depending on individual's attitude to work

A recent study suggests the importance of individual differences. A rat study compared the effects of amphetamines and caffeine on cognitive effort. First of all, giving the rats the choice of easy or hard visuospatial discriminations revealed that, as with humans, individuals could be divided into those who tended to choose difficult trials ("workers") and those who preferred easy ones ("slackers"). (Easy trials took less effort, but earned commensurately smaller reward.)

Amphetamine, it was found, made the slackers worked harder, but made the workers take it easier. Caffeine, too, made the workers slack off, but had no effect on slackers.

The extent to which this applies to humans is of course unknown, but the idea that your attitude to cognitive effort might change how stimulants affect you is an intriguing one. And of course this is a more general reminder that factors, whatever they are, have varying effects on individuals. This is why it's so important to have a large sample size, and why, as an individual, you can't automatically assume that something will benefit you, whatever the research says.

Cocker, P. J., Hosking J. G., Benoit J., & Winstanley C. A. (2012). Sensitivity to Cognitive Effort Mediates Psychostimulant Effects on a Novel Rodent Cost|[sol]|Benefit Decision-Making Task. Neuropsychopharmacology.

http://the-scientist.com/2012/03/28/stimulants-fail-to-stimulate/

Effects of caffeine vary with quantity and gender

Two recent studies suggest that caffeine is most effective in boosting your energy and alertness in small doses, and more effective for males.

A study involving 80 college students (34 men and 46 women) between the ages of 18 and 40, has found that those given a caffeinated energy drink reported feeling more stimulated and less tired than those given a decaffeinated soda or no drink. However, although reaction times were

faster for those consuming caffeine than those given a placebo drink or no drink, reaction times slowed for increasing doses of caffeine, suggesting that smaller amounts of caffeine are more effective.

The three caffeine groups were given caffeine levels of either 1.8 ml/kg, 3.6 ml/kg or 5.4 ml/kg. The computerized "go/no-go" test which tested their reaction times was given half an hour after consuming the drinks.

In another study, 52 children aged 12-17 drank flattened Sprite containing caffeine at four concentrations: 0, 50 mg, 100 mg or 200 mg. Changes in blood pressure and heart rate were then checked every 10 minutes for one hour, at which point they were given a questionnaire and an opportunity to eat all they wanted of certain types of junk food.

Interestingly, there were significant gender differences, with boys drinking high-caffeine Sprite showing greater increases in diastolic blood pressure (the lower number) than boys drinking the low-caffeine Sprite, but girls being unaffected. Boys were also more inclined to report consuming caffeine for energy or "the rush", than girls were.

Those participants who ingested the most caffeine also ate more high-sugar snack foods in the laboratory, and reported higher protein and fat consumption outside the lab.

Howard, M. A., & Marczinski C. A. (2010). Acute Effects of a Glucose Energy Drink on Behavioral Control. Experimental and Clinical Psychopharmacology. 18(6), 553 - 561.

Temple, J. L., Dewey A. M., & Briatico L. N. (2010). Effects of Acute Caffeine Administration on Adolescents. Experimental and Clinical Psychopharmacology. 18(6), 510 - 520.

http://www.eurekalert.org/pub_releases/2010-12/apa-im120210.php

Coffee consumption associated with higher cognitive performance in older women

A study of 1528 older adults compared cognitive function (assessed by 12 standardized tests), and lifetime and current coffee consumption (self-reported).

Higher lifetime coffee consumption in women was associated with better performance on six of 12 tests; current caffeinated coffee intake was associated with better performance on two tests. Among women aged 80 or more years, lifetime coffee intake was associated with better performance on 11 of the 12 tests, but the results did not reach statistical significance. There was no relation between cognitive function and decaffeinated coffee intake.

No relation was found between coffee intake and cognitive function among men.

A study investigating the effects of caffeine on homocysteine levels also found that the effects of caffeine were stronger in women.

Johnson-Kozlow, M., Kritz-Silverstein, D., Barrett-Connor, E. & Morton, D. 2002. Coffee Consumption and Cognitive Function among Older Adults. *American Journal of Epidemiology*, 156(9), 842-50.

Habituation to caffeine

Summary

Caffeine reduces blood flow in the brain. The size of the reduction is greater in heavy coffee drinkers. Caffeine withdrawal increases blood flow, and again, the effect is greater in heavy drinkers.

The beneficial effect of caffeine on exercise endurance was substantially greater for nonhabitual users.

Nonhabitual coffee drinkers needed a low dose of caffeine for their optimal performance on cognitive tasks while coffee drinkers and smokers needed a higher dose.

Caffeine increased blood pressure in nonhabitual coffee drinkers, but not habitual coffee drinkers, indicating that a tolerance to the effects of coffee occurs.

High caffeine users performed more poorly on a verbal reasoning task. Interactions between caffeine, time of day, and user history, support the view that different cognitive processes are affected differently by these three factors.

All doses of caffeine significantly affected cognitive performance, with little difference between the sizes of dose. The effects were more marked in those with a higher level of habitual caffeine intake.

A study of older adults found higher lifetime consumption of caffeinated coffee was associated with better performance on several cognitive tests — for women, but not men.

Conclusion: While people clearly build up a tolerance to some of the effects of caffeine, it is not yet clear what the long-term effects of regular caffeine use are. Nor can we say, as yet, what factors are important in determining those long-term effects, although we can speculate that gender, age, metabolic factors, cardiovascular health, alcohol and tobacco use are all possible influences.

News reports

Caffeine's effect on blood flow in the brain

A recent imaging study of 20 healthy adults, half of whom were classified as heavy caffeine users, has demonstrated that an amount of caffeine equal to what's in two to three cups of coffee can constrict blood vessels and reduce blood flow in the gray matter areas of the brain.

In heavy caffeine users blood flow was reduced by 26% and in light caffeine users, by 19%. During withdrawal (achieved by abstention from caffeine for at least 30 hours), the blood flow in the heavy caffeine users was more than 30% greater than in the light caffeine users experiencing withdrawal.

Field, A.S., Laurienti, P.J., Yen, Y.F., Burdette, J.H. & Moody, D.M. 2003. Dietary caffeine consumption and withdrawal: confounding variables in quantitative cerebral perfusion studies? *Radiology, 27(1)*, 129-35.

Caffeine increases exercise endurance, especially for nonhabitual users

Many studies have demonstrated that caffeine ingested before physical activity causes rapid and significant improvement in performance, especially in aerobic exercise capacity. Because most researchers have assumed the effect is related to the circulating level of the caffeine in the bloodstream, it has been assumed that the maximum effects are found one hour after consumption.

In the present study, 21 volunteers of both sexes, with a mean age of 32, and active in aerobic events, rode a cycle ergometer to exhaustion on six occasions, after being given either a placebo or 5 mg/kg of caffeine. Exercise to exhaustion was completed once per week at either one, three or six hours after taking either the placebo or caffeine. Participants were asked to refrain from heavy exercise and alcohol for 24 hours before each trial, and to refrain from caffeine for 12 hours beforehand.

It was found that caffeine significantly improved the time to exhaustion for all participants, but the effect was distinctly greater for those unaccustomed to caffeine (e.g., at one hour, average exercise time was some 27.4 minutes for users having caffeine, compared to 23.3 for users on placebo; and 32.7 minutes for non-users having caffeine, compared to 24.2 for non-users on placebo). Exercise times were greater for users at both one and three hours after taking caffeine, but not at six hours. For non-users, however, the effects of caffeine were still found six hours after ingestion.

Heart rates were consistently higher for non-users, and increased further after caffeine consumption. Caffeine produced a small but significant increase in oxygen consumption after 15 minutes of exercise for both users and non-users, and in non-users, also slightly raised glucose levels (already slightly higher than that of users).

http://www.eurekalert.org/pub_releases/2002-07/aps-dt071502.php

Bell, D.G. & McLellan, T.M. 2002. Exercise Endurance 1, 3, and 6 Hours After Caffeine Ingestion in Caffeine Users and Non-users. *Journal of Applied Physiology, 93*, 1227-1234.

More caffeine needed for habituated users

Sixteen volunteers who were classified as either non-smokers and non-coffee drinkers; smokers and coffee drinkers; non-smokers and coffee drinkers, participated in a Greek study of the effect of caffeine on the central nervous system and cardiorespiratory system. Cognitive tasks were undertaken after taking 90 and 250 mg of caffeine on two separate days. Participants abstained from caffeine for a week before the study.

The study found that non-coffee drinkers needed a low dose of caffeine for their optimal performance while coffee drinkers and smokers needed a higher dose of caffeine for optimal performance. A higher dose significantly increased the blood pressure for non-coffee drinkers.

Kourtidou-Papadeli C, Papadelis C, Louizos AL, Guiba-Tziampiri O. 2002. Maximum cognitive performance and physiological time trend measurements after caffeine intake. *Cognitive Brain Research, 13(3)*, 407-15.

Everyday use of caffeine

Study confirms validity of laboratory tests to naturalistic settings

The study investigated whether a more realistic coffee-drinking regime (4 doses of 65 mg over a 5 hour period) produced the same effects as a single large dose of caffeine (200 mg). The smaller doses produce an equivalent amount of caffeine present in the body after 5 hours. 24 participants attended four sessions. On two of the sessions, coffee was consumed at 10am, 11am, 12 noon and 1pm. In one of these sessions 65 mg caffeine was added to the decaffeinated coffee. In the other two sessions, the coffee was consumed at 1pm and 200 mg caffeine was added in one of the sessions. Participants completed a battery of mood and performance tests at 9.30am and 3pm.

Regardless of whether the caffeine was consumed in one big hit or in several, smaller doses, caffeine led to increased alertness, increased anxiety, and improved performance on a variety of cognitive tasks: simple and choice reaction tasks, a cognitive vigilance task, a task requiring sustained response and a dual task involving tracking and target detection.

Brice, C.F. & Smith, A.P. 2002. Effects of caffeine on mood and performance: a study of realistic consumption. *Psychopharmacology, 164*, 188-192.

The effect of low doses of caffeine on cognition

This study looked at the effects of low doses of caffeine, more typical of tea or cola drinks. The 23 participants were given either 0, 12.5, 25, 50 or 100 mg of caffeine. Their performance was tested once before and three times after the placebo or caffeine.

All doses of caffeine significantly affected cognitive performance, with little difference between the sizes of dose. The effects were more marked in those with a higher level of habitual caffeine intake.

Smit, H.J. & Rogers, P.J. 2000. Effects of low doses of caffeine on cognitive performance, mood and thirst in low and higher caffeine consumers. *Psychopharmacology, 152*, 167-173.

The effects of caffeine in doses typical of one cup of tea

There is little evidence concerning the effects of caffeine in doses typical of one cup of tea. The present study investigated the effect of 60 mg caffeine, consumed in either tea or hot water, on cognitive performance in 8 males. Over four test sessions, participants consumed a different hot beverage (tea or hot water, either caffeinated or not), and then completed some nine tests.

Reaction time on pattern recognition, delayed match to sample, and match to sample visual search, was significantly faster for those who had caffeine.

Durlach, P.J. 1998. The effects of a low dose of caffeine on cognitive performance. *Psychopharmacology, 140 (1)*, 116-119.

Caffeine helps ameliorate factors that lower cognitive performance

Summary

Caffeinated drinks can largely overcome the declining cognitive performance seen over the course of the day, most particularly in older people. However, such effects are not thought to be solely due to caffeine, nor are the effects necessarily any better that any stimulant would produce, such as sugar, or exercise.

High doses of caffeine improved vigilance, choice reaction time, and motor learning, in fit young men who were sleep deprived and stressed. In another study, a high dose of caffeine improved some cognitive functions for some of a 64-hour sleep deprivation period, and improved others for all the 64 hour period.

Caffeine in a carbohydrate electrolyte solution improved cognitive performance in male athletes after strenuous exercise.

Conclusion: Caffeine is helpful in ameliorating the effects of time of day and sleep deprivation on cognitive performance. In normal circumstances (i.e., not prolonged sleep deprivation, or extreme stress), caffeine seems to be more helpful to older adults.

News reports

Circadian Rhythm

Coffee helps older adults retain mental sharpness later in the day

Memory in most older adults often depends on the time of day, with memory typically optimal early in the morning and declining during the late afternoon. A study of 40 older adults (over 65) confirmed the popular belief in the value of caffeine in helping overcome this decline in mental sharpness later in the afternoon. All the participants (like three-quarters of all people in that age group, studies suggest) described themselves as "morning people". Testing confirmed that they were less alert later in the day.

The participants, who were already regular coffee drinkers (and were asked to abstain before arriving for the test), were given the California Verbal Learning Test at 8 a.m. and again at 4 p.m., on two days, separated by an interval of 5 to 11 days. During these sessions, some were given a mug of regular coffee, and others a mug of decaffeinated coffee. Interestingly, those given regular coffee performed a little better in the morning than those who had decaffeinated, but the really striking result was that those on regular coffee performed as well on the afternoon tests as they had done in the morning.

While it is good news that this daily decline can be overcome so easily, we cannot conclude from this that the caffeine was responsible. As the researcher noted, any stimulant may work as effectively. Anything that supplies a boost in energy, such as having sugar, or going for a brisk walk, may have the same effect.

http://www.nytimes.com/2002/01/01/health/psychology/01AGIN.html

Ryan, L., Hatfield, C. & Hofstetter, M. 2002. Caffeine Reduces Time-of-Day Effects on Memory Performance in Older Adults. *Psychological Science, 13(1),* 68-71.

Effects of age, caffeine & time of day on psychomotor and cognitive function

This study assessed the influence of age on the effects of caffeine on a variety of psychomotor, cognitive and subjective tests. The 48 participants, of both sexes, were from two different age groups: 20-25 years and 50-65 years. They were all regular moderate caffeine drinkers. Half of each group was given a placebo, and the other half 250 mg of caffeine. A range of tests was used to assess psychomotor, cognitive and subjective functioning before treatment and 1 hour after.

Unsurprisingly, before treatment, the younger participants generally performed better than the older on psychomotor and cognitive tests. After taking the placebo, performance and alertness improved in the younger group but declined in the older. After caffeine, both groups showed an improvement in psychomotor and cognitive performance, particularly in offsetting the declining performance over time in the older participants.

Rees, K., Allen, D. & Lader, M. 1999. The influences of age and caffeine on psychomotor and cognitive function. *Psychopharmacology, 145 (2)*, 181-188.

Caffeine prevents normal decline in alertness over day

Nineteen volunteers drank black tea, coffee, caffeinated water, decaffeinated tea or plain water on three occasions through the day (at 9am, 2pm, and 7pm). A variety of psychometric tests, including a short-term memory test, were carried out at regular intervals through the day.

The drinking of tea rather than water, and of caffeinated compared to decaffeinated beverages, largely prevented the steady decline in alertness and cognitive capacity observed among those drinking plain water. In other words, caffeinated drinks largely overcame normal time-of-day effects. However, the benefit of decaffeinated tea suggests that this is not simply due to the caffeine. Other factors may involve other substances in the drinks, or psychological factors.

Hindmarch, I., Quinlan, P.T., Moore, K.L. & Parkin, C. 1998. The effects of black tea and other beverages on aspects of cognition and psychomotor performance. *Psychopharmacology (Berl), 139(3)*, 230-8.

Effects of caffeine and time of day on study

The effects of caffeine on several study-related tasks were investigated in 25 students (6 males, 19 females). The tasks involved short-term memory, mental arithmetic, reading comprehension, serial search and verbal reasoning, and took place in eight sessions, at four times of day (1am, 7am, 1pm, 7pm), after participants were given caffeine (4 mg/kg) or a placebo. Participants were classified according to their self-reported caffeine consumption.

Caffeine improved performance on all speed-related tasks. High caffeine users performed more poorly than the others on the verbal reasoning task. Interactions between caffeine, time of day, and user history, support the view that different cognitive processes are affected differently by these three factors.

Mitchell, P.J. & Redman, J.R. 1992. Effects of caffeine, time of day and user history on study-related performance. *Psychopharmacology (Berl), 109*, 121-6.

Sleep Deprivation

Caffeine can mitigate effects of stress and sleep deprivation on cognitive performance

A study of 68 U.S. Navy Sea-Air-Land (SEAL) trainees examined whether moderate doses of caffeine would reduce adverse effects of sleep deprivation and exposure to severe environmental and operational stress on cognitive performance.

The participants were given capsules of either 100, 200, or 300 mg caffeine or placebo, after 72 hours of sleep deprivation and continuous exposure to other stressors. A variety of cognitive tests were administered, involving vigilance, reaction time, working memory and motor learning.

As expected, sleep deprivation and environmental stress had an adverse effect on performance. The higher doses of caffeine (200 and 300 mg) significantly improved visual vigilance, choice reaction time, and motor learning, with the greatest effects on tests of vigilance and reaction time. The greatest effects of caffeine were present after an hour, but significant effects persisted for 8 hours.

Lieberman, H.R., Tharion, W.J., Shukitt-Hale, B., Speckman, K.L. & Tulley, R. 2002. Effects of caffeine, sleep loss, and stress on cognitive performance and mood during U.S. Navy SEAL training. Sea-Air-Land. *Psychopharmacology (Berl), 164*, 250-61.

The mitigating effects of caffeine on sleep deprivation

Sixteen men participated in this study to determine whether slow-release caffeine (SRC) could mitigate the effects of sleep deprivation on vigilance and cognitive performance. Participants were kept awake for 64 hours, and given either a 300mg SRC or a placebo twice a day.

Cognitive function was assessed using a variety of tests. It was found that those receiving the caffeine were more vigilant throughout the period of sleep deprivation, while the cognitive functions showed a variety of patterns: some improved up until the 33rd hour; others were ameliorated through the entire period; alertness was better from the thirteenth hour.

Beaumont, M., Batejat, D., Pierard, C., Coste, O., Doireau, P., Van Beers, P., Chauffard, F., Chassard, D., Enslen, M., Denis, J.B. & Lagarde, D. 2001. Slow release caffeine and prolonged (64-h) continuous wakefulness: effects on vigilance and cognitive performance. *Journal of Sleep Research, 10(4)*, 265-76.

Strenuous Exercise

Caffeine improves cognitive performance after strenuous physical exercise

On five separate occasions, 15 male athletes were given either one of three carbohydrate electrolyte solutions (CES), a CES placebo, or water. They drank part of the drink before, and the rest during, an all-out 1 hour time trial on a bicycle ergometer. The three CES drinks contained various levels of caffeine (150, 225 and 320 mg/l). Cognitive tests were carried out immediately before and after the exercise.

Before the exercise, the low dose caffeine CES improved long-term memory. Immediately after the vigorous exercise, all cognitive functions were improved by the low- and medium-dose caffeine drinks.

Hogervorst, E., Riedel, W.J., Kovacs, E., Brouns, F. & Jolles, J. 1999. Caffeine improves cognitive performance after strenuous physical exercise. *International Journal of Sports Medicine, 20*, 354-61.

Caffeine helps protect against Alzheimer's

Summary

While animal studies support the value of regular caffeine consumption in reducing the risk of developing Alzheimer's disease, human studies have been less consistent.

There is some evidence that benefits may be restricted to women.

News reports

Why coffee helps protect against Alzheimer's disease

Support for the value of coffee in decreasing the risk of Alzheimer's comes from a mouse study, which found that an as yet unidentified ingredient in coffee interacts with caffeine in such a way that blood levels of a growth factor called GCSF (granulocyte colony stimulating factor) increases. GCSF is a substance greatly decreased in patients with Alzheimer's disease and demonstrated to improve memory in Alzheimer's mice.

The finding points to the value of caffeinated coffee, as opposed to decaffeinated coffee or to other sources of caffeine. Moreover, only "drip" coffee was used; the researchers caution that they don't know whether instant caffeinated coffee would provide the same GCSF response.

There are three ways that GCSF seems to improve memory performance in the Alzheimer's mice: by recruiting stem cells from bone marrow to enter the brain and remove beta-amyloid protein; by increasing the growth of new synapses; by increasing neurogenesis.

The amount of coffee needed to provide this protection, however, is estimated to be about 4 to 5 cups a day. The researchers also believe that this daily coffee intake is best begun at least by middle age (30s – 50s), although starting even in older age does seem to have some protective effect.

Weirdly (I thought), the researchers remarked that "The average American gets most of their daily antioxidants intake through coffee". Perhaps this points more to the defects in their diet than to the wonders of coffee! But the finding is consistent with other research showing an association between moderate consumption of coffee and decreased risk of Parkinson's disease, Type II diabetes and stroke.

A just-completed clinical trial has investigated GCSF treatment to prevent Alzheimer's in patients with mild cognitive impairment, and the results should be known soon.

Bayer-Carter, J. L., Green P. S., Montine T. J., VanFossen B., Baker L. D., Watson S. G., et al. (2011). Diet Intervention and Cerebrospinal Fluid Biomarkers in Amnestic Mild Cognitive Impairment. Arch Neurol. 68(6), 743 - 752.

Cao, C., Wang, L., Lin, X., Mamcarz, M., Zhang, C., Bai, G., Nong, J., Sussman, S. & Arendash, G. 2011.Caffeine Synergizes with Another Coffee Component to Increase Plasma GCSF: Linkage to Cognitive Benefits in Alzheimer's Mice. Journal of Alzheimer's Disease, 25(2), 323-335.

http://www.eurekalert.org/pub_releases/2011-06/jaaj-dca061011.php
http://www.eurekalert.org/pub_releases/2011-06/uosf-mii062011.php

Animal studies indicate caffeine may slow dementia and cognitive decline but human studies less conclusive

Several recent studies and reviews suggest that the benefits of caffeine for age-related cognitive impairment and dementia are limited. It may be that the association only exists for women.

A special supplement in the Journal of Alzheimer's Disease focuses on the effects of caffeine on dementia and age-related cognitive decline. Here are the highlights:

A mouse study has found memory restoration and lower levels of amyloid-beta in Alzheimer's mice following only 1-2 months of caffeine treatment. The researchers talk of " a surprising ability of moderate caffeine intake to protect against or treat AD", and define moderate intake as around 5 cups of coffee a day(!).

A review of studies into the relation between caffeine intake, diabetes, cognition and dementia, concludes that indications that coffee/caffeine consumption is associated with a decreased risk of Type 2 diabetes and possibly also with a decreased dementia risk, cannot yet be confirmed with any certainty.

A study involving 351 older adults without dementia found the association between caffeine intake and cognitive performance disappeared once socioeconomic status was taken into account.

A study involving 641 older adults found caffeine consumption was significantly associated with less cognitive decline for women only. Supporting this, white matter lesions were significantly fewer in women consuming more than 3 units of caffeine per day (after adjustment for age) than in women consuming less.

A Portuguese study involving 648 older adults found that caffeine intake was associated with a lower risk of cognitive decline in women, but not significantly in men.

A review of published studies examining the relation between caffeine intake and cognitive decline or dementia shows a trend towards a protective effect of caffeine, but because of the limited number of epidemiological studies, and the methodological differences between them, is unable to come up with a definitive conclusion.

A review of published epidemiological studies looking at the association between caffeine intake and Parkinson's Disease confirms that higher caffeine intake is associated with a lower risk of developing Parkinson's Disease (though this association may be stronger for men than women).

Other studies provide evidence of caffeine's potential in treatment, improving both the motor deficits and non-motor symptoms of Parkinson's.

Arendash, G.W. & Cao, C. Caffeine and Coffee as Therapeutics Against Alzheimer's Disease. Journal of Alzheimer's Disease, 20 (Supp 1), 117-126.
Biessels, G.J. Caffeine, Diabetes, Cognition, and Dementia. Journal of Alzheimer's Disease, 20 (Supp 1), 143-150.
Kyle, J., Fox, H.C. & Whalley, L.J. Caffeine, Cognition, and Socioeconomic Status. Journal of Alzheimer's Disease, 20 (Supp 1), 151-159.
Ritchie, K. et al. Caffeine, Cognitive Functioning, and White Matter Lesions in the Elderly: Establishing Causality from Epidemiological Evidence. Journal of Alzheimer's Disease, 20 (Supp 1), 161-161
Santos, C. et al. Caffeine Intake is Associated with a Lower Risk of Cognitive Decline: A Cohort Study from Portugal. Journal of Alzheimer's Disease, 20 (Supp 1), 175-185.
Santos, C. et al. Caffeine Intake and Dementia: Systematic Review and Meta-Analysis. Journal of Alzheimer's Disease, 20 (Supp 1), 187-204.
Costa, J. et al. Caffeine Exposure and the Risk of Parkinson's Disease: A Systematic Review and Meta-Analysis of Observational Studies. Journal of Alzheimer's Disease, 20 (Supp 1), 221-238.
Prediger, R.D.S. Effects of Caffeine in Parkinson's Disease: From Neuroprotection to the Management of Motor and Non-Motor Symptoms. Journal of Alzheimer's Disease, 20 (Supp 1), 205-220.

Full text available at http://iospress.metapress.com/content/t13614762731/.
http://www.eurekalert.org/pub_releases/2010-05/ip-nec051710.php

Caffeine reverses memory impairment in Alzheimer's mice

Consistent with earlier indications that moderate caffeine consumption may protect against memory decline, a study of genetically engineered mice has found that when the old mice began to show memory impairment, those given caffeine for 2 months performed as well as normal aged mice on cognitive tests, while those given plain drinking water continued to do poorly. The Alzheimer's mice received the equivalent of five 8-oz. cups of regular coffee a day (or two cups of Starbucks coffee, or 14 cups of tea). Moreover, the brains of the caffeinated mice showed nearly a 50% reduction in levels of beta amyloid. The effect appears to be through suppression of both β-secretase and presenilin 1 /g-secretase expression. Caffeine had this effect only on those with Alzheimer's; normal mice given caffeine through adulthood showed no cognitive benefit.

Arendash, G.W. et al. 2009. Caffeine Reverses Cognitive Impairment and Decreases Brain Amyloid-β Levels in Aged Alzheimer's Disease Mice. Journal of Alzheimer's Disease, 17 (3), 661-680.

Cao, C. et al. 2009. Caffeine Suppresses Amyloid-β Levels in Plasma and Brain of Alzheimer's Disease Transgenic Mice. Journal of Alzheimer's Disease, 17 (3), 681-697.

http://www.eurekalert.org/pub_releases/2009-07/uosf-crm070109.php

Midlife coffee drinking reduces risk of dementia

A large, long-running Finnish study has found that those who were coffee drinkers at midlife had lower risk for dementia and Alzheimer's later in life compared to those drinking no or only little coffee midlife. The lowest risk was found among moderate coffee drinkers (drinking 3-5 cups of coffee/day). Tea drinking was relatively uncommon and was not associated with dementia.

Eskelinen, M.H. et al. 2009. Midlife Coffee and Tea Drinking and the Risk of Late-Life Dementia: A Population-based CAIDE Study. Journal of Alzheimer's Disease, 16(1).

http://www.physorg.com/news151225794.html

Caffeine and blood pressure

Summary

High blood pressure in older adults (58 years and older) is associated with an increased risk of age-related cognitive impairment, of severe cognitive decline, of dementia and Alzheimer's.

A study found that caffeine intake equivalent to four or five cups of coffee raised blood pressure an average of five points.

More recently, research suggests that it may be something other than caffeine in the coffee, that raises blood pressure.

Conclusion: High blood pressure is undoubtedly a risk factor for cognitive decline and dementia for those over 60. While coffee raises blood pressure, it is not clear that caffeine is the culprit. Older adults with blood pressure problems should therefore also avoid decaffeinated coffee.

News reports

Coffee's effect on blood pressure doesn't depend on caffeine content

A Swiss study of 15 volunteers aged 27-38, of whom 6 were habitual coffee drinkers, found that an intravenous injection of caffeine increased blood pressure and muscle sympathetic nervous activity (MSA) in both habitual and nonhabitual coffee drinkers (by 29% after 30 minutes and 53% after 60 minutes). (Sympathetic nervous system activity plays an important role in the regulation of blood pressure and over-activation has been linked with high blood pressure.)

Nonhabitual coffee drinkers had a similar result an hour after drinking a triple espresso, whether regular or decaffeinated. However, habitual coffee drinkers experienced only the increase in MSA, without the increase in blood pressure.

The effect of decaffeinated coffee on nonhabitual coffee drinkers suggests that some ingredient or ingredients other than caffeine is responsible for the cardiovascular activation.

The lack of BP effect on habitual coffee drinkers indicates that a tolerance to the effects of coffee occurs, but the fact that sympathetic nerve activation still occurred in this group indicates that the tolerance is to other ingredients in the coffee, not caffeine.

Recent epidemiological studies have produced conflicting results on whether or not regular coffee drinking is good for the cardiovascular system. This study suggests that, if coffee is indeed beneficial for the heart and arteries, it is not an effect of the caffeine.

The researchers suggest that coffee drinking may not be hazardous for those with normal blood pressure, but more importantly, the results suggest that those with hypertension should avoid decaffeinated coffee as well as regular coffee.

http://www.eurekalert.org/pub_releases/2002-11/aha-nbo111302.php

http://www.americanheart.org/presenter.jhtml?identifier=3006582

Corti, R., Binggeli, C., Sudano, I., Spieker, L., Hänseler, E., Ruschitzka, F., Chaplin, W.F., Lüscher, T.F. & Noll, G. 2002. Coffee Acutely Increases Sympathetic Nerve Activity and Blood Pressure Independently of Caffeine Content: Role of Habitual Versus Nonhabitual Drinking. *Circulation, 106*, 2935-2940.

Moderate Caffeine Use Boosts Blood Pressure

Laboratory studies have made it clear that caffeine raises blood pressure, but the current study demonstrates what happens in real life. 19 habitual coffee drinkers wore blood-pressure monitors while they went about their normal working routine. It was found that caffeine intake equivalent to four or five cups of coffee raised blood pressure an average of five points, compared to days when they only had one cup. The effect occurred within an hour of consumption, and the subjects' blood pressure remained elevated throughout the day. Participants also reported higher levels of stress during the day when they received the higher caffeine dose, and they showed a corresponding increase in heart rate.

A review of nine major studies of blood-pressure and cardiovascular-disease risk showed that a 5-point difference in diastolic blood pressure was associated with at least a 34% increase in the incidence of stroke and a 21% increase in the incidence of coronary heart disease.

http://www.eurekalert.org/pub_releases/1998-05/DUMC-DRFT-240598.php

Lane, J.D., Phillips-Bute, B.G. & Pieper, C.F. 1998. Caffeine raises blood pressure at work. *Psychosomatic Medicine, 60*, 327-330.

Background: The connection between high blood pressure and cognitive performance

Treatment to lower blood pressure reduces risk of cognitive decline in stroke patients.

"White-matter lesions" start to appear in the brain from around 60 years, and are responsible for some of the decline in cognitive function related to aging. Such lesions are also linked with circulatory problems, including hypertension.

Raised systolic blood pressure, particularly in conjunction with high cholesterol levels, increases the risk of Alzheimer’s.

High blood pressure is a risk factor for cognitive decline in those aged 58 or older.

Those with untreated high blood pressure are at greater risk of severe cognitive decline.

News reports

High blood pressure linked to memory problems in middle age

A study involving nearly 20,000 people age 45 and older, of whom nearly half were taking medication for high blood pressure, has found that those with high diastolic blood pressure (the bottom number of a blood pressure reading) were more likely to have cognitive impairment than those with normal diastolic readings. For every 10 point increase in the reading, the odds of a person having cognitive problems was 7% higher. There was no correlation with systolic blood pressure. The results were adjusted for age, smoking status, exercise level, education, diabetes and high cholesterol. High diastolic blood pressure is known to lead to weakening of small arteries in the brain.

Tsivgoulis, G. et al. 2009. Association of higher diastolic blood pressure levels with cognitive impairment. *Neurology, 73*, 589-595.

A diet that may reduce age-related cognitive decline

The Dietary Approaches to Stop Hypertension (DASH) diet lowers blood pressure and is often recommended by physicians to people with high blood pressure or pre-hypertension. An 11-year study of over 3800 seniors found that those with higher DASH diet adherence scores had higher cognitive scores at the beginning of the study and increasingly so over time. Four of the nine food-group/nutrient components were independently associated with cognitive scores -- vegetables, whole grains, low-fat dairy, nut/legumes. When a score based on just these four components was used, the difference between those in the highest quintile and those in the lowest was even greater, particularly by the end of the study.

Wengreen, H.J. et al. 2009. DASH diet adherence scores and cognitive decline and dementia among aging men and women: Cache County study of Memory Health and Aging. Presented at the Alzheimer's Association International Conference on Alzheimer's Disease July 11-16 in Vienna.

Factors helping you maintain cognitive function in old age

An 8-year study of over 2,500 seniors in their 70s, has found that 53% showed normal age-related decline, 16% showed major cognitive decline, and an encouraging 30% had no change or improved on the tests over the years. The most important factors in determining whether a person maintained their cognitive health was education and literacy: those with a ninth grade literacy level or higher were nearly five times as likely to stay sharp than those with lower literacy levels; those with at least a high school education were nearly three times as likely to stay sharp as those who have less education. Lifestyle factors were also significant: non-smokers were nearly twice as likely to stay sharp as smokers; those who exercised moderately to vigorously at least once a week were 30% more likely to maintain their cognitive function than those who do not exercise that often; people working or volunteering and people who report living with someone were 24% more likely to maintain cognitive function.

Yaffe, K. et al. 2009. Predictors of maintaining cognitive function in older adults: The Health ABC Study. *Neurology, 72*, 2029-2035.

High blood pressure may make it difficult for the elderly to think clearly

A study involving 36 community-dwelling elderly (60-87 years old) whose blood pressure and cognitive functioning was monitored for 60 days has found that those with high blood pressure tended to perform more poorly on one of the three cognitive tasks, and this was particularly so when their blood pressure was higher than normal. The finding suggests that high blood pressure impacts on inductive reasoning, and thus the ability to work flexibly with unfamiliar information and find solutions. It also suggests that, for those with high blood pressure, such reasoning will be particularly difficult when they are stressed.

Gamaldo, A.A., Weatherbee, S.R. & Allaire, J.C. 2008. Exploring the Within-Person Coupling of Blood Pressure and Cognition in Elders. *Journal of Gerontology: Psychological Science, 63*, 386-389.

High blood pressure associated with risk for mild cognitive impairment

A study of nearly 1000 older adults (average age 76.3) without mild cognitive impairment at the start of the study found that over the follow-up period (average: 4.7 years), 334 individuals developed mild cognitive impairment, of which 160 were amnestic (reduced memory) and 174 were non-amnestic. Hypertension (high blood pressure) was associated with an increased risk of non-amnestic mild cognitive impairment; but not with amnestic mild cognitive impairment.

Reitz, C. et al. 2007. Hypertension and the Risk of Mild Cognitive Impairment. *Archives of Neurology, 64(12)*, 1734-1740.

Memory tasks require more coordinated brain blood flow for people with high blood pressure

Previous studies have found an association between high blood pressure and cognitive decline in older adults, but the evidence hasn't been entirely consistent. Now a new study helps explain why the situation is not entirely straightforward. It appears that people with high blood pressure required more blood flow to the parts of the brain that support memory function than those with normal blood pressure. Moreover, and surprisingly, it turned out that antihypertensive medication actually made it worse, increasing the inefficiency of the brain's work during memory tasks.

Jennings, J.R. et al. 2007. Paper presented at the American Heart Association's 61st Annual Fall Conference of the Council for High Blood Pressure Research.

Lowering blood pressure doesn't prevent cognitive impairment, dementia

A review of three large-scale studies of patients with hypertension who were treated with either medication or lifestyle strategies found no convincing evidence that lowering blood pressure prevents the development of dementia or cognitive impairment in hypertensive patients without apparent prior cerebrovascular disease. However, there is some evidence that midlife hypertension but not late life hypertension is related to cognitive decline; these studies involved patients aged 60 and older.

McGuiness, B., et al. The effects of blood pressure lowering on development of cognitive impairment and dementia in patients without apparent prior cerebrovascular disease. *The Cochrane Database of Systematic Reviews 2006, Issue 2*.

Review supports link between lifestyle factors and cognitive function in older adults

A review of 96 papers involving 36 very large, ongoing epidemiological studies in North America and Europe looking at factors involved in maintaining cognitive and emotional health in adults as they age has concluded that controlling cardiovascular risk factors, such as reducing blood pressure, reducing weight, reducing cholesterol, treating (or preferably avoiding) diabetes, and not smoking, is important for maintaining brain health as we age. The link between hypertension and cognitive decline was the most robust across studies. They also found a consistent close correlation between physical activity and brain health. However, they caution that more research is needed before specific recommendations can be made about which types of exercise and how much exercise are beneficial. They also found protective factors most consistently reported for cognitive health included higher education level, higher socio-economic status, emotional support, better initial performance on cognitive tests, better lung capacity, more physical exercise, moderate alcohol use, and use of vitamin supplements. Psychosocial factors, such as social disengagement and depressed mood, are associated with both poorer cognitive and emotional health in late life. Increased mental activity throughout life, such as learning new things, may also benefit brain health.

Hendrie,H.C. et al. 2006. The NIH Cognitive and Emotional Health Project: Report of the Critical Evaluation Study Committee. *Alzheimer's & Dementia, 2(1),* 12-32.

Uncontrolled high blood pressure means more cognitive problems in old age

A study involving a subset of men (average age 67 years) in the VA Normative Aging Study has found that those men with uncontrolled hypertension performed significantly worse on tests of verbal fluency and short-term memory. Those whose hypertension was controlled did as well as those with normal blood pressure. In the United States, hypertension affects 60% of adults age 60 and older, and a high proportion of these are untreated or inadequately treated.

Brady, C.B., Spiro, A. III & Gaziano, J.M. 2005. Effects of Age and Hypertension Status on Cognition: The Veterans Affairs Normative Aging Study. *Neuropsychology, 19 (6).*

High blood pressure has stronger effect on cognitive function in African-Americans

Analysis of a large longitudinal study (the Maine-Syracuse Longitudinal Study 1976—2002) has found significant associations of high blood pressure to lower cognitive performance in the areas of abstract reasoning, psychomotor skills and visual organization skills. This association, moreover, was significantly greater for African-Americans, although it should be noted that there were only 147 African-Americans among the 1,563 participants. The effect was independent of age.

Robbins, M.A., Elias, M.F., Elias, P.K. & Budge, M.M. 2005. Blood Pressure and Cognitive Function in an African-American and a Caucasian-American Sample: The Maine-Syracuse Study. *Psychosomatic Medicine, 67 (5),* 707-714.

High blood pressure may be a factor in "senior moments"

An imaging study of seniors (average age 60) found that those with high blood pressure showed reduced blood flow to active brain areas when performing various everyday memory tasks, such as looking up a phone number then walking to another room to pick up the phone and dial the number. The diminished blood flow correlated to slightly worse scores on the memory tests. The

differences weren't large, but may help account for "senior moments" - memory problems commonly associated with age. It's estimated that as many as a third of those with high blood pressure are not aware they have it.

Jennings, J.R., Muldoon, M.F., Meltzer, C.C., Ryan, C. & Price, J. 2003. Human Cerebral Blood Flow Responses to Information Processing Tasks are Decreased in Hypertensives Relative to Normotensives. Report presented at the American Heart Association's 57th Annual High Blood Pressure Research Conference, September 23.

Effects of high blood pressure on cognition may have been overstated

Epidemiological studies have suggested hypertensive patients perform worse than individuals with normal blood pressure on cognition tests. A new study has investigated performance on specific cognitive tasks (visual and memory search involving computer displays) by those with high blood pressure who were not on medication and had no detectable cardiovascular disease. Participants ranged in age from 20 to 80. Contrary to expectation, high blood pressure slowed performance only in the middle-aged group (40-59), not in those younger or older.

Madden, D., Langley, L., Thurston, R., Whiting, W. & Blumenthal, J.2003. *Aging, Neuropsychology and Cognition*.

Treatment to lower blood pressure reduces risk of cognitive decline in stroke patients

High blood pressure and stroke are associated with increased risks of dementia and cognitive impairment. In a study aimed to determine whether blood pressure lowering would reduce the risks of dementia and cognitive decline among individuals with cerebrovascular disease, 6105 people with prior stroke or transient ischemic attack were given either active treatment (perindopril for all participants and indapamide for those with neither an indication for nor a contraindication to a diuretic) or matching placebo(s). Over some 4 years, dementia was found in 6.3% of those given active treatment and 7.1% of those in the placebo group. Cognitive decline occurred in 9.1% of the actively treated group and 11.0% of the placebo group. The researchers concluded that blood pressure lowering with perindopril and indapamide therapy was helpful for those with cerebrovascular disease, in terms of reduced risks of dementia and cognitive decline.

The PROGRESS Collaborative Group* 2003. Effects of Blood Pressure Lowering With Perindopril and Indapamide Therapy on Dementia and Cognitive Decline in Patients With Cerebrovascular Disease. *Archives of Internal Medicine, 163*, 1069-1075.

Age-related changes in the brain's white matter affect cognitive function

From around age 60, "white-matter lesions" appear in the brain, significantly affecting cognitive function. But without cognitive data from childhood, it is hard to know how much of the difference in cognitive abilities between elderly individuals is due to aging. A longitudinal study has been made possible by the Scottish Mental Survey of 1932, which gave 11-year-olds a validated cognitive test. Scottish researchers have tracked down healthy living men and women who took part in this Survey and retested 83 participants. Testing took place in 1999, when most participants were 78 years old. It was found that the amount of white-matter lesions made a significant contribution to general cognitive ability differences in old age, independent of prior ability. The amount of white-matter lesions contributed 14.4% of the variance in cognitive scores; early IQ

scores contributed 13.7%. The two factors were independent.
Although white-matter lesions are viewed as a normal part of aging, they are linked with other health problems, in particular to circulatory problems (including hypertension, diabetes, heart disease and cardiovascular risk factors).

Deary, I.J., Leaper, S.A., Murray, A.D., Staff, R.T. & Whalley, L.J. 2003. Cerebral White Matter Abnormalities and Lifetime Cognitive Change: A 67-Year Follow-Up of the Scottish Mental Survey of 1932. Psychology and Aging, 18 (1), 140-8

Raised systolic but not diastolic blood pressure increases risk of Alzheimer's

A large-scale Finnish study found that raised systolic blood pressure and high serum cholesterol concentration, particularly in combination, in midlife, increase the risk of Alzheimer's disease in later life. Raised diastolic blood pressure had no significant effect.
http://www.bmj.com/cgi/content/full/322/7300/1447

Kivipelto, M., Helkala**,** E., Laakso, M.P., Hänninen, T., Hallikainen, M., Alhainen, K., Soininen, H., Tuomilehto, J. & Nissinen, A. 2001. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ, 322*, 1447-1451.

High blood pressure increases cognitive decline in older adults

A large-scale six-year study of people aged 40 to 70 years old found that people with diabetes and high blood pressure are more likely to experience cognitive decline. Diabetes was associated with greater cognitive decline for those younger than 58 as well as those older than 58, but high blood pressure was a risk factor only for the 58 and older group.
http://www.eurekalert.org/pub_releases/2001-01/MC-Nsld-0701101.php
http://www.eurekalert.org/pub_releases/2001-01/AAoN-Dahb-0801101.php

Knopman, D., Boland, L.L., Mosley, T., Howard, G., Liao, D., Szklo, M., McGovern, P. & Folsom, A.R. 2001. Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology, 56*, 42-48.

Untreated high blood pressure important factor in cognitive decline in old age

A large-scale study of French people aged 59 to 71 found that, after four years, 21.7% of those with untreated high blood pressure experienced severe cognitive decline. Of those with high blood pressure whose treatment didn't bring the blood pressure down to normal, 12.5% had severe cognitive decline. Of those whose high blood pressure was successfully treated, 7.8% had severe cognitive decline. Only 7.3% of those with normal blood pressure had severe cognitive decline.
http://www.eurekalert.org/pub_releases/1999-12/AAoN-Hbpi-091299.php

Tzourio, C., Dufouil, C., Ducimetière, P. & Alpérovitch, A. 1999. Cognitive decline in individuals with high blood pressure: A longitudinal study in the elderly. *Neurology, 53*, 1948.

Caffeine and homocysteine levels

Summary

Older adults with very high homocysteine levels perform more poorly on cognitive tests, and are at significantly greater risk of a stroke, of developing vascular dementia, and Alzheimer's.

Brewed coffee raises homocysteine levels.

A recent study suggests that caffeine is only one of the substances in brewed coffee that raises homocysteine levels.

Conclusion: High homocysteine levels in older adults increase the risk of cognitive decline and dementia. Coffee raises homocysteine levels, but, as caffeine doesn't appear to be the only ingredient in coffee responsible for this effect, it would seem wise to avoid decaffeinated brewed coffee as well.

News reports

Contribution of caffeine to the homocysteine-raising effect of coffee

Coffee drinking raises homocysteine levels. Elevated levels of homocysteine are associated with a greater risk of stroke, vascular dementia, and Alzheimer's disease.

While it is known that brewed coffee raises homocysteine levels, it is unclear which ingredients are responsible. In this study, 48 heavy coffee drinkers, of both sexes and ranging in age from 19 to 65, were given either: (1) 6 capsules providing 870mg of caffeine, (2) 4 cups of strong filtered coffee that contained 870 mg of caffeine, or (3) 6 placebo capsules. Each treatment lasted two weeks. Blood samples were drawn fasting and four hours after 2 cups of coffee or 3 capsules. ("Heavy" is defined as consuming 6 or more cups of coffee a day). 31% of the subjects were smokers, who are known to metabolize caffeine more rapidly than non-smokers.

Compared to placebo, the caffeine capsules raised the average fasting homocysteine level by 5%, while the brewed coffee lifted the level 11%. Four hours after consumption of two cups of brewed coffee, homocysteine levels had risen 19%, compared to only 4% for the caffeine capsules. The effects of caffeine were stronger in women, but there was no significant gender difference for coffee.

It would appear then, that while caffeine is partly responsible for the homocysteine-raising effect of coffee, it is by no means the primary factor.

http://www.eurekalert.org/pub_releases/2002-11/ajoc-cde112002.php

Verhoef, P., Pasman, W.J., van Vliet, T., Urgert, R. & Katan, M.B. 2002. Contribution of caffeine to the homocysteine-raising effect of coffee: a randomized controlled trial in humans. *American Journal of Clinical Nutrition, 76*, 1244-8.

Background: The connection between homocysteine levels and cognitive performance

Elevated levels of homocysteine in older adults have been found to be associated with a more than five-fold increase in the risk for stroke, a nearly five-fold risk for vascular dementia, and almost triple the risk for Alzheimer's disease.

A large-scale study found older adults with very high homocysteine levels performed more poorly on cognitive tests.

High levels of homocysteine appear to hurt brain function through their effect on blood vessels in the brain.

News reports

B-vitamin deficiency may cause vascular cognitive impairment

A new mouse study helps clarify the association between homocysteine, folate & B12, and cognitive impairment. The study found that mice fed a diet deficient in folate and vitamins B12 and B6 demonstrated significant deficits in spatial learning and memory compared with normal mice, developed plasma homocysteine concentrations that were seven-fold higher, and showed smaller capillary length and density in blood vessels in the hippocampus. Homocysteine is produced by the breakdown of a dietary protein called methionine; B-vitamins are required to convert homocysteine back to methionine. A third group of mice were fed a diet enriched with methionine. These mice showed similar, but less pronounced effects. The findings indicate that increased levels of homocysteine, produced by low intake of folate and B vitamins, impairs cognition through microvascular changes.

Troen, A.M. et al. 2008. B-vitamin deficiency causes hyperhomocysteinemia and vascular cognitive impairment in mice. Proceedings of the National Academy of Sciences, 105, 12474-12479.

Preventing high levels of homocysteine may protect against age-related cognitive impairment

Previous studies have found a link between high levels of homocysteine and poor cognitive performance, but it has been difficult to work out just what the association is, in view of confounding factors such as cardiovascular risk factors and levels of folate, B12, and B6, all of which play a role in high levels of homocysteine. A new analysis has disentangled these factors, and has found that, in people over 60 (but not those under 60), higher levels of homocysteine are independently associated with lower levels of cognitive performance. Similarly, higher levels of vitamin B12 are associated with higher levels of cognitive performance. The researchers suggest vitamins B12, B6, and folate taken before 60 could help protect against later cognitive impairment.

Elias, M.F., Sullivan, L.M., D'Agostino, R.B., Elias, P.K., Jacques, P.F., Selhub, J., Seshadri, S., Au, R., Beiser, A. & Wolf, P.A. 2005. Homocysteine and Cognitive Performance in the Framingham Offspring Study: Age Is Important. *American Journal of Epidemiology, 162*, 644-653.

Homocysteine, genotype, and risk for stroke, vascular dementia, and Alzheimer's

A study of 83 Alzheimer's patients, 78 patients with vascular dementia, 64 stroke patients, and 71 healthy controls, found that elevated levels of homocysteine were associated with a more than five-fold increase in the risk for stroke, a nearly five-fold risk for vascular dementia, and almost triple the risk for Alzheimer's disease. High blood levels of homocysteine have been found to be associated with an increased heart attack risk in several studies. High levels of homocysteine have been found to be associated with deficiencies in vitamin B12 and folate, and also with smoking.
http://www.eurekalert.org/pub_releases/2002-10/aha-mhh092602.php

McIlroy, S.P., Dynan, K.B., Lawson, J.T., Patterson, C.C. & Passmore, A.P. 2002. Moderately Elevated Plasma Homocysteine, Methylenetetrahydrofolate Reductase Genotype, and Risk for Stroke, Vascular Dementia, and Alzheimer Disease in Northern Ireland. *Stroke, 33,* 2351 – 2356.

Plasma homocysteine as a risk factor for dementia and Alzheimer's disease

Findings from the long-running Framingham study found people with elevated levels of homocysteine in the blood had nearly double the risk of developing Alzheimer's disease (AD). This study is the first to tie homocysteine levels measured several years before with later diagnosis of AD and other dementias, and provides the most powerful evidence yet of the link between high homocysteine levels and AD.
http://www.eurekalert.org/pub_releases/2002-02/nioa-hhl021202.php

Seshadri, S., Beiser, A., Selhub, J., Jacques, P.F., Rosenberg, I.H., D'Agostino, R.B., Wilson, P.W.F. & Wolf, P.A. 2002. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *The New England Journal of Medicine, 346*, 476-483.

Hyperhomocysteinemia associated with poor recall

Recent studies have linked Alzheimer disease and dementia after multiple strokes to extremely high serum homocysteine concentrations. A survey of 1299 men and women aged 60 and over, none of who had previously had a stroke, found an independent relationship between very high homocysteine levels and poor performance on cognitive tests. The folate status of the participants was checked as folate has been shown to significantly modify homocysteine levels. Story recall was worse among subjects with a combination of low folate and high homocysteine than in those whose homocysteine levels were normal or low. Homocysteine levels increased with age and were accompanied by a comparable decline in folate status. The researchers found independent associations between the highest levels of homocysteine and poorer recall. Among subjects with the highest level of homocysteine, the odds of passing a word delayed-recall test were identical whether their folate status was high or low.
http://www.eurekalert.org/pub_releases/2001-04/AJoC-Hhla-2504101.php

Morris, M.S., Jacques, P.F., Rosenberg, I.H. & Selhub, J. 2001. Hyperhomocysteinemia associated with poor recall in the third National Health and Nutrition Examination Survey. *American Journal of Clinical Nutrition, 73*, 927-933.

Caffeine and glucose levels

Summary

Evidence for the effect of caffeine on glucose regulation is inconclusive as yet, and I would not include this section except that it throws a somewhat murky light on the complexity of the caffeine — cognition relationship. In particular:

The suggestion that caffeine may be a risk factor for impaired glucose tolerance is interesting in light of recent discoveries into the relationship between glucose and the brain.

The suggestion that coffee has a different effect on habitual users, who may have built up tolerance to certain factors, than it does on non-habitual users.

The suggestion that coffee may contain some substances that have a beneficial effect, and others that have a negative effect.

The evidence that glucose can have a beneficial or a negative effect on cognitive function, depending on dosage and the individual.

News reports

High coffee consumption linked to lower risk of diabetes

The possible association between coffee consumption and type 2 diabetes was investigated in a large population-based study of 17,111 Dutch people aged 30-60 years. It was found that those who drank at least seven cups a day were only half as likely to develop type 2 diabetes as those who drank two cups or fewer. The risk of type 2 diabetes decreased with higher coffee consumption in a graded manner.

Consumption of tea was lower than that of coffee, and was not associated with diabetes risk. Consumption of decaffeinated coffee was too low to study separately.

The association remained after removal of possible confounding factors. Moreover, higher coffee consumption was associated with generally unfavourable factors: a low educational level, a higher body-mass index, cigarette smoking, alcohol use, less leisure time physical activity, and a generally less favourable diet.

While caffeine acutely lowers insulin sensitivity, tolerance could develop. The long-term effects are unknown. In an intervention study[1], increased coffee consumption for 14 days reduced fasting plasma glucose, whereas substitution of regular coffee for decaffeinated coffee for 20 days did not affect plasma glucose. That study did not include a control group, but the results suggested that components of coffee other than caffeine could be beneficial for glucose metabolism.

As well as caffeine, coffee contains substantial amounts of magnesium, which has been associated with a lower risk of type 2 diabetes[2].

van Dam, R.M. & Feskens, E.J.M. 2002. Coffee consumption and risk of type 2 diabetes mellitus. *Lancet, 360,* 1477-78.

1 Naismith, D.J., Akinyanju, P.A., Szanto, S. & Yudkin, J. 1970. The effect in volunteers of coffee and decaffeinated coffee on blood glucose, insulin, plasma lipids and some factors involved in blood clotting. *Nutr Metabol 12,* 144-51.

2 Salmerón, J., Manson, J.E., Stampfer, M.J., Colditz, G.A., Wing, A.L. & Willett, W.C. 1997. Dietary fiber, glycemic load, and risk of non-insulin dependent diabetes mellitus in women. *JAMA, 277,* 472-77.

Caffeine reduces glucose intake

On two occasions, seven men performed one-legged knee extensor exercises for an hour, before being given, two hours later, either caffeine (5 mg/kg) or a placebo. An hour later, glucose uptake was tested.

Insulin-stimulated glucose uptake was significantly reduced in those who had caffeine. However, this could be offset to some extent by exercise.

Thong, F.S.L., Derave, W., Kiens, B., Graham, T.E., Ursø, B., Wojtaszewski, J.F.P., Hansen, B.F. & Richter, E.A. 2002. **C**affeine-Induced Impairment of Insulin Action but Not Insulin Signaling in Human Skeletal Muscle Is Reduced by Exercise. *Diabetes, 51,* 583-590.

Caffeine may decrease insulin sensitivity

Caffeine or placebo was administered intravenously to 12 healthy volunteers. Caffeine was found to decrease insulin sensitivity by 15%.

Keijzers, G.B., De Galan, B.E., Tack, C.J. & Smits, P. 2002. Caffeine Can Decrease Insulin Sensitivity in Humans. *Diabetes Care, 25,* 364-369.

Caffeine may increase glucose levels

A study of the effects of caffeine on glucose tolerance involved 30 nonsmoking healthy adults aged 26-32 who abstained from coffee and all other foods containing caffeine for at least four weeks. Participants were then given either 50 mL of decaffeinated cold coffee without sugar or 50 mL of the same decaffeinated coffee with 200 mg of caffeine added (no change in taste or color). Two weeks later, those who had previously received the caffeine were given the placebo and vice versa. The coffee was followed by 75g of oral glucose.

The 200 mg of caffeine increased blood glucose levels at the third and fourth hour of the oral glucose tolerance test (OGTT).

Pizziol, A., Tikhonoff, V., Paleari, C.D. et al. 1998. Effects of Caffeine on Glucose Tolerance: A Placebo Controlled Study. *European Journal of Clinical Nutrition, 52,* 846-849.

Background: The connection between blood sugar levels and cognitive performance

The brain runs on glucose. It used to be thought that, unless a person is starving, the brain always received an ample supply of glucose. However, recent research has now demonstrated that glucose levels fall in those parts of the brain that are active during particular tasks$_1$.

The drop in glucose levels appears to be greater in older subjects, and also takes longer to recover[2].

The ability to get glucose from the blood to the tissues (including the brain) is reduced in diabetes.

Impaired glucose tolerance (IGT) refers to a condition in which blood sugar levels are higher than normal, but are not high enough to be classified as diabetes. In the U.S., about 40-45% of older adults (65 years or older) have either type 2 diabetes or IGT.

Impaired glucose tolerance is a risk factor for cardiovascular disease[3].

A study of non-diabetic middle-aged and elderly people found that those with impaired glucose tolerance had a smaller hippocampus and scored worse on tests for recent memory.

It is speculated that in individuals with impaired glucose tolerance, during periods of increased metabolic demand (such as while trying to remember something), glucose levels drop in the parts of the brain doing the work, leading to memory problems.

Glucose has been shown to help memory for prose in healthy older adults. While this has been less clear in younger adults, it now appears that glucose can aid memory in younger adults if the task is sufficiently difficult.

However, it appears that the effective dose range is rather narrow, with too much glucose impairing, rather than enhancing, cognitive functions. The effective amount depends on the individual — their metabolism and the glucose level in their brains at the time.

News reports

Poor glucose control linked to cognitive impairment in diabetics

The ongoing Memory in Diabetes (MIND) study, involving some 3,000 type 2 diabetics 55 years and older, has found that cognitive functioning abilities drop as average blood sugar levels rise. However, there was no connection between daily blood glucose levels and cognitive performance. The study adds to growing evidence that poorer blood glucose control is strongly associated with poorer memory function, that may eventually lead to mild cognitive impairment, vascular dementia and Alzheimer's disease. It is also possible that people with impaired cognitive ability are less compliant in taking medications and controlling their diabetes. Further research will test the hypothesis that improving glucose control results in improved cognitive function.

Cukierman-Yaffe, T. et al. 2009. Relationship Between Baseline Glycemic Control and Cognitive Function in Individuals With Type 2 Diabetes and Other Cardiovascular Risk Factors: The Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) trial. *Diabetes Care, 32 (2)*, 221-226.

Blood sugar linked to normal cognitive aging

Following research showing that decreasing brain function in the area of the hippocampus called the dentate gyrus is a main contributor of normal age-related cognitive decline, an imaging study has been investigating the cause of this decreasing function by looking at measures that typically change during aging, like rising blood sugar, body mass index, cholesterol and insulin levels. The

study of 240 community-based nondemented elders (average age 80 years), of whom 60 had type 2 diabetes, found that decreasing activity in the dentate gyrus only correlated with levels of blood glucose. The same association was also found in aging rhesus monkeys and in mice. The finding suggests that maintaining blood sugar levels, even in the absence of diabetes, could help maintain aspects of cognitive health. It also suggests that one reason why physical exercise benefits memory may be its effect on lowering glucose levels.

Wu, W. et al. 2008. The brain in the age of old: The hippocampal formation is targeted differentially by diseases of late life. *Annals of Neurology, 64 (6)*, 698-706.

Diabetic seniors may experience memory declines after eating high-fat food

Growing evidence links diabetes to cognitive impairment. Now a small study of 16 adults (aged 50 years and older) with type 2 diabetes compared their cognitive performance on three separate occasions, fifteen minutes after consuming different meals. One meal consisted of high fat products – a danish pastry, cheddar cheese and yogurt with added whipped cream; the second meal was only water; and the third was the high-fat meal plus high doses of vitamins C (1000 mg) and E (800 IU) tablets. Researchers found that vitamin supplementation consistently improved recall scores relative to the meal alone, while those who ate the high fat meal without vitamin supplements showed significantly more forgetfulness of words and paragraph information in immediate and time delay recall tests. Those on water meal and meal with vitamins showed similar levels in cognitive performance. The finding indicates not only that diabetics can temporarily further worsen already underlying memory problems associated with the disease by consuming unhealthy meals, but also that this can be remedied by taking high doses of antioxidant vitamins C and E with the meal, suggesting that the effect of high-fat foods si to cause oxidative stress. However, this is hardly a recommended course of action, and the real importance of this finding is that it emphasizes the need for diabetics to consume healthy foods high in antioxidants, like fruits and vegetables. Of course, this is a very small study, and further replication is needed.

Chui, M.H. & Greenwood, C.E. 2008. Antioxidant vitamins reduce acute meal-induced memory deficits in adults with type 2 diabetes. *Nutrition Research, 28 (7)*, 423-429.

High sugar blood levels linked to poor memory

A new study takes an important step in explaining cognitive impairment in diabetics, and suggests a possible cause for some age-related memory impairment. The study assessed non-diabetic middle-aged and elderly people. Those with impaired glucose tolerance (a pre-diabetic condition) had a smaller hippocampus and scored worse on tests for recent memory. These results were independent of age or overall cognitive performance.

The study raises the possibility that exercise and weight loss, which help control blood sugar levels, may be able to reverse some of the memory loss that accompanies aging.
http://www.eurekalert.org/pub_releases/2003-02/nyum-hsb013003.php

Convit, A., Wolf, O.T., Tarshish, C. & de Leon, M.J. 2003. Reduced glucose tolerance is associated with poor memory performance and hippocampal atrophy among normal elderly. *Proceedings of the National Academy of Sciences USA, 100 (4)*, 2019-2022.

Glucose improves semantic memory in older adults

On four sessions separated by a week, healthy older adults were given glucose or saccharin immediately before hearing a narrative prose passage, or immediately before being tested for recall of the passage (24 hours after training).

Participants recalled significantly more information after taking the glucose rather than saccharin, irrespective of whether the glucose was given before learning or before recall.

Manning, C.A., Stone, W.S., Korol, D.L. & Gold, P.E. 1998. Glucose enhancement of 24-h memory retrieval in healthy elderly humans. *Behavioural Brain Research, 93 (1-2)*, 71-6.

Glucose can help semantic memory in younger adults

Although earlier evidence suggested that glucose does not enhance cognitive function in healthy young adults, more recent findings suggest that glucose can be effective when the tests are sufficiently difficult. In college students, glucose consumption significantly enhanced memory of a prose passage. Glucose also appeared to enhance attentional processes in these students. Neither face and word recognition nor working memory was influenced by glucose treatment.

Korol, D.L. & Gold, P.E. 1998. Glucose, memory, and aging. *American Journal of Clinical Nutrition, 67(4)*, 764S-771S.

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1. McNay, E.C., Fries, T.M. & Gold, P.E. 2000. Decreases in rat extracellular hippocampal glucose concentration associated with cognitive demand during a spatial task. *Proceedings of the National Academy of Sciences USA, 97(6)*, 2881-5.

2. McNay, E.C. & Gold, P.E. 2001. Age-related differences in hippocampal extracellular fluid glucose concentration during behavioral testing and following systemic glucose administration. *Journals of Gerontology A: Biological Sciences and Medical Sciences, 56(2)*, B66-71.

3. Tominaga, M., Eguchi, H., Manaka, H., Igarashi, K., Kato, T. & Sekikawa, A. 1999. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. *Diabetes Care, 22(6)*, 920-4.

Glossary

aMCI: mild cognitive impairment, amnesic subtype; patients with this disorder show memory impairments but not other cognitive impairments (e.g., in reasoning).

amyloid beta peptides : these fragments of amyloid beta are the main protein component of plaques, and probably a major cause for the their toxicity. They are thought to bind to a receptor in the brain, blocking the signals needed for learning and memory. The peptides come in two forms: A-beta 42 and A-beta 40. Amyloid beta peptides routinely circulate in the human bloodstream, where they are harmless. Early beta amyloid accumulation within neurons is the trigger for the onset of memory decline in Alzheimer's.

apolipoprotein E (APoE): is a protein whose main responsibility is transporting cholesterol out of the cell. Too much of this protein results in an increase in the level of free cholesterol in the cells. An allele of the gene responsible for this protein has been identified as a major genetic risk factor for Alzheimer's.

beta-amyloid plaques: are considered one of the hallmarks of Alzheimer's disease. The plaques are hard, insoluble aggregations of various peptides and proteins, chiefly and most important amyloid-beta peptides. Recent research suggests plaques attach primarily to blood vessels, damaging them.

cerebrospinal fluid (CSF): a clear salty liquid which cushions the brain

homocysteine: is a homologue of the naturally-occurring amino acid cysteine, produced from methionine. Elevated levels of homocysteine are associated with a greatly increased risk for coronary heart disease, stroke, vascular dementia, and Alzheimer's disease. Levels of homocysteine in the blood are strongly influenced by diet — high levels are particularly associated with deficiencies in vitamin B12 and folate — lifestyle factors such as smoking, and genetic factors.

methionine: is an amino acid found in beta-amyloid; suggested as being the source of the toxic free radicals produced by amyloid-beta peptides. Methionine is one of the essential amino acids that we require from food. Broken down, it produces homocysteine; B-vitamins are required to convert homocysteine back to methionine. High levels of methionine can be found in sesame seeds, Brazil nuts, fish, meats, and dairy products. Most fruits and vegetables contain very little -- spinach, potatoes, and boiled corn are some of the exceptions.

neurogenesis: creation of new neurons; common in young brains, it has only recently been found to occur in adult brains, and then only in specific regions.

The **Stroop test** is a method of studying automatic processing, and is one of the most commonly used diagnostic tools when determining an attention problem. In the most common form of the test, participants see color words (*e.g.*, blue) printed in either the color the word refers to, or in another color, such as red. When the print color is different from the word, participants usually take longer to name the print color than when word and color match.

Vigilance is perceptual rather than cognitive, and has been defined as the simultaneous preconscious monitoring of all sensory channels for events that will require a shift in attention, as attention to those stimuli of relevance to you, and as the ability to disregard much of the stimulation one receives.

white matter : Brain tissue is divided into two types: gray matter and white matter. White matter is made up of the axons of neurons -- the long filaments that extend from the cell bodies and carry the electrical signals that carry the messages between neurons. It's the myelin sheathing that makes it look white. There are three major white matter systems, which all connect to form one continuous system: cortical white matter; the corpus callosum; the internal capsule.

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