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Reviewing the effects of dietary salt on cognition: mechanisms and future directions

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ABSTRACT

Background and Objectives: Consumption of salt exceeds dietary guidelines for many countries around the world, despite efforts to increase awareness of the potential cardiovascular health risks. Emerging evidence, primarily from rodent models, indicates that high salt intake may also impair aspects of cognitive function. To our knowledge, here we provide the first review of the effects of salt on cognition. To review literature on the effects of high-salt diets on cognitive measures across human and non-human animal research to generate targeted questions for future studies. **Methods and Study Design:** Non-systematic literature review of studies manipulating (in rodents) or measuring (in humans) salt intake and assessing performance on cognitive measures. **Results:** Studies in humans have focused on older populations and show mixed associations between salt intake and cognitive performance. By contrast, most rodent studies have found impairments in cognition following chronic consumption of high-salt (typically 7-8%) diets. Most report impairments in tasks assessing spatial memory with corresponding increases in hippocampal oxidative stress and inflammatory responses originating in the gut. Notably, several rodent studies reported that high-salt diets impaired cognitive function in the absence of blood pressure changes. **Conclusions:** Contrasting results from human and animal studies emphasise the need for further studies to clarify whether salt intake affects cognition. Testing cognition in high-salt diet models that induce hypertension will increase the translatability of future studies in rodents. A challenge for research in humans is isolating the effects of salt from those of fat and sugar that tend to co-occur in 'western' diets.

Key Words: dietary salt, cognition, rodent, obesity, hypertension

The current global state of salt intake

Salt is a ubiquitous component of most modern diets around the world. Recent studies indicate that salt consumption remains high throughout the Asia-Pacific region in countries including Australia (9.6 g/day¹), China (9.1 g/day²), Japan (11 g/day³) and India (9.45-10.41 g/day⁴). These estimated intakes are almost double the WHO's recommended maximum daily salt intake of 5 g/day, and around 50-fold greater than that of our ancestors, who consumed minimal or no salt until farming practices developed during the Neolithic period fostered its widespread use as a preservative, taste enhancer and, more recently, key ingredient in processed foods.⁵ Alarming, high salt consumption in contemporary societies extends to school children, with a recent Australian study estimating that 72% consumed more than the

recommended upper limit.⁶ High salt intake continues across many regions despite concerted health policy initiatives to raise awareness of the associated health risks (e.g. World Action on Salt & Health [WASH]) and the fact that over 75 countries have now adopted strategies to reduce population salt intake by 30% by 2025.⁷

Health concerns related to excess dietary salt have traditionally focused on its relationship with hypertension and the increased risk of stroke and cardiovascular disease.⁸ One modelling study estimated that in 2010, 1.65 million deaths from cardiovascular disease, globally, were attributable to high salt consumption.⁹ While the consensus remains that salt intake is associated with cardiovascular harm, Mente et al¹⁰ recently argued that the detrimental effects of salt intake hold only in countries with mean intake of more than 5 g/day. However, others have questioned this interpretation until further evidence can be gathered from randomised-controlled trials.¹¹

High salt intake is also associated with an increased risk of renal disease, stomach cancer and osteoporosis,¹² and results from MRI studies suggest that excessive salt intake may promote cerebral small vessel disease by increasing white matter hyperintensity,¹³ and increase autoimmune responses in the CNS by enhancing the activity of pro-inflammatory T-cells, cytokines and macrophages.¹⁴ A recent study in mice found that a high-salt diet (4% NaCl in solid diet supplemented with 1% NaCl in drinking water, vs 0.5% NaCl control diet) profoundly affected faecal microbiome diversity via specific depletion of the *Lactobacillus murinus* bacterial group.¹⁵ In contrast to this study,¹⁵ which found no effect of salt on body weight, Lanaspa and colleagues¹⁶ found that mice given access to a 1% NaCl solution (also containing the non-nutritive sweetener sucralose [0.04%]) for 30-weeks exhibited increased body weight, fat mass and liver triglycerides. Separate experiments showed that access to 1% NaCl solution exacerbated the detrimental metabolic effects of (a) 15% fructose solution and (b) a high-fat, high-sugar ‘western’ style solid diet.¹⁶ High salt consumption therefore appears to exert broad systemic effects, increasing the risk of metabolic disease and impaired brain function as well as cardiovascular complications.

Investigation of the relationship between dietary salt and cognition

Taken together, these results raise the interesting possibility that high levels of salt consumption may affect aspects of cognitive function. Most research on the effects of dietary salt on cognition in humans (summarised in Table 1) has been generated from longitudinal studies of ageing populations, with mixed results. A 3-year prospective study of 1262 adults aged 67-84 found that lower sodium intake at baseline was associated with improved

cognitive performance in the Mini-Mental State Examination (MMSE) over time.¹⁷ However, this association only held in participants reporting low levels of physical activity at baseline, with no relationship between salt and cognitive performance in more active participants. A small observational study of 44 adults (mean age 57) found that participants with lower MMSE scores reported significantly higher salt intakes than those with higher scores.¹⁸ By contrast, two prospective studies in older adults^{19, 20} reported no association between dietary salt intake (assessed via food frequency questionnaires) and cognitive decline measured by the MMSE (Nowak et al., 2018; 1,194 adults, mean age 74±3; 6.9 year follow-up)¹⁸ or on measures of mild cognitive impairment and pre-dementia in women with hypertension or on antihypertensive medication (Haring et al., 2016; 6,426 women aged 65-79; median follow-up 9.1 years).¹⁹ In the latter study, cognitive impairment was strongly associated with hypertension, suggesting that effects of salt on cognition might be mediated by changes to vascular function.¹⁹

Associations between salt intake and cognitive function have also been assessed in cross-sectional studies. Rush and colleagues²¹ reported that low salt intake was associated with poorer performance on the MMSE and impaired executive functioning (as assessed by the Trails-B task) in a community sample of 925 adults aged 50-96 (see Table 1). Conversely, two smaller studies where sodium intake was estimated from biomarkers (rather than using FFQs) have shown associations with cognitive impairment assessed using the MMSE. The first found that 24-h urinary sodium excretion was negatively associated with MMSE scores in 119 adults (mean age 54.2±16.1 [SD])²² while the second reported that serum sodium was negatively correlated with MMSE scores in 82 older adults (mean age 87±6).²³

Attempts to isolate the cognitive effects of salt consumption per se are made difficult by the fact that salt intake is closely (and positively) associated with total energy intake in human populations.^{16,17} Total energy intake is an important moderator of the relationship between sodium intake and hypertension, leading some to suggest dietary sodium density as a relevant metric.²⁴ Whereas most studies control for total energy intake in their analyses,^{17,20,21} others have not measured or adjusted for this factor.^{18,22} In addition, differences in total energy intake likely correspond to higher intakes of refined carbohydrates and saturated fats that are themselves associated with cognitive impairment.²⁵ Taken together, this highlights a need for research testing the effects of salt consumption under tightly controlled conditions.

Cognitive effects of dietary salt in animal models

Animal models allow for the relationship between dietary salt intake and cognitive function to be tested with strict control over other aspects of the diet. The results of these experiments are summarised in Table 2. In contrast to the mixed results from studies in humans, most studies in rodents have found adverse cognitive effects of high salt intake, with impairments often linked to oxidative stress markers. For example, Liu and colleagues²⁶ reported that mice fed a high-salt diet for 12 weeks (7% NaCl vs 0.4% in controls) exhibited impaired spatial memory performance, assessed by the Morris Water Maze, and increased oxidative stress in the hippocampus, but not in the surrounding neocortex. Another study found poorer place recognition memory and long-term contextual fear memory in mice fed a high-salt diet (8% NaCl vs 0.4% control diet) for 7 weeks.²⁷ These cognitive impairments were accompanied by increased oxidative stress and downregulation of synaptic protein and plasticity markers in the hippocampus. A comparable study in rats found that nine weeks' consumption of a high-salt diet (8% NaCl vs 0.26% control diet) impaired spatial memory in the Morris Water Maze and in a contextual fear conditioning paradigm.²⁸ Rats exposed to the high-salt diet in this study exhibited reduced cerebral blood flow and lower synaptogenesis in the hippocampus relative to controls. Similarly, Chugh et al (2013) reported poorer spatial memory in a water-based radial arm maze and reduced levels of the antioxidant enzyme glyoxalase-1 in the hippocampus of aged rats fed a high-salt diet (8% NaCl vs 0.4% control diet) for 4 weeks, with no effects in younger animals.²⁹

Salt, cognition and gut inflammation

A paper recently published in Nature Neuroscience³⁰ brings a new perspective to this question. Faraco and colleagues found that the cognitive impairments produced by a high-salt diet were linked to an altered immune response originating in the gut. Mice fed a diet up to 16 times higher in salt than their control counterparts (4 or 8% NaCl vs 0.5% control diet) were impaired in several tests designed to measure spatial and non-spatial memory.³⁰ The high-salt diet increased gut T-helper lymphocytes in the small intestine; these cells produce the pro-inflammatory cytokine interleukin-17, which was increased in the circulation. Faraco and colleagues suggest that these immune changes in the gut increase susceptibility of the brain to autoimmune responses, linked to suppressed anti-inflammatory actions of regulatory T cells. The high-salt diet also led to severe hypoperfusion³⁰ of the brain, suggesting that compromised delivery of oxygen and nutrients may also contribute to adverse cognitive effects. Notably, vascular changes such as these have also been linked to the impaired cognition seen in

patients with advanced diabetes – so-called vascular dementia.³¹ These new data support the notion that the gut immune response to dietary manipulations can have dramatic impacts on brain function, providing further support for a role for the ‘Gut-brain axis’ in cognition.

The cognitive effects of high-salt diets have also been tested in genetic models of salt sensitivity. The Dahl rat model of salt sensitivity was developed by selectively breeding male and female Sprague-Dawley rats for their blood pressure response to a high-salt diet.³² Whereas salt-resistant Dahl rats remain normotensive on high-salt diets, the salt-sensitive strain develops hypertension rapidly and even exhibit gradual increases in blood pressure on normal-salt diets.³³ One study testing cognitive performance within this model found that exposure to a high-salt diet (8% NaCl for 7 weeks) impaired spatial learning and memory in the Morris water maze and working memory in the radial arm maze in the salt-sensitive but not the salt-resistant strain, with no impairments in inhibitory learning.³⁴ By contrast, Ruiz-Opazo and colleagues (2004) compared the effects of regular (0.4% NaCl) and low-salt diets (0.008% NaCl) on cognition in salt-sensitive and resistant Dahl rats. Surprisingly, when salt-sensitive rats were fed a low-salt diet – one which normalises hypertension – they exhibited impaired performance on measures of social recognition memory and socially-transmitted food preference.³⁵ By contrast, feeding a low-salt diet improved spatial memory in the Morris Water Maze for the salt-resistant strain, while novel object recognition memory was intact in both strains, regardless of diet.³⁵ Thus, while detrimental effects of high-salt diets on cognition have been demonstrated both in outbred strains and in genetic models of salt-sensitivity, the effects of salt restriction require further investigation, particularly in view of evidence that salt restriction may bring about adverse cardiovascular effects³⁶ and induce acute symptoms of fatigue and anhedonia.³⁷

In summary, the balance of evidence from animal models indicates that prolonged exposure to diets high in salt can impair cognition, mostly on hippocampal-dependent measures of learning and memory. These effects are in many cases linked to enhanced oxidative stress and inflammation in the CNS. Novel evidence indicates that these effects are mediated through an inflammatory response originating in the gut³⁰ and changes to the gut microbiome.¹⁵ Figure 1 presents an overview of the potential adverse effects of dietary salt on cognition, and other health outcomes, in the rodent and human literature reviewed here.

Caveats and considerations

Care should be exercised when attempting to extrapolate these results to human populations. A key consideration is that rodent studies typically administer 4-12 weeks of exposure to salty

diets that contain 15-20 times as much salt than those fed to control animals (Table 2). By contrast, estimates of population-level salt intake in humans are generally around double the WHO recommendation of 5 g/day. Nonetheless, given that the effects of high salt intake may accumulate across the lifespan, longer-term experimental studies in rodents using lower concentrations are warranted, particularly in light of recent evidence suggesting that the link between salt intake and cardiovascular complications holds only for countries where population consumption averages over 5 g/day.¹⁰ In rodent studies, even the salt content contained in control diets (typically between 0.3 and 0.5%) may be well above biological needs, given evidence that rats ingest only 15% of this amount when allowed to freely consume a 0.5% NaCl solution alongside a salt-free solid diet and water.³⁸

A second consideration is that in some rodent studies, high-salt diets have produced cognitive impairments without altering blood pressure,^{26,27,30} whereas others have shown cognitive deficits alongside hypertension^{28,29} (Table 2). This suggests that hypertension is not required for salt-induced cognitive dysfunction. Since high salt intake is robustly linked to hypertension in humans, further animal work is needed to delineate the effects of high salt intake from its cardiovascular sequelae, and to identify potentially distinct mechanisms impairing cognitive performance independent of blood pressure changes. Clearly, accurate determination of blood pressure responses is key in this regard. A critical third variable is obesity, which is associated with both hypertension³⁹ and cognitive decline.⁴⁰ Yet, as for hypertension, most rodent studies reviewed here have found no effects of salt on body weight gain,^{26,28-30} with two exceptions reporting increased¹⁶ and decreased weight²⁷ in high-salt groups relative to controls. Clearly, further work is required to delineate the effects of salt on the triad of body weight, hypertension, and cognition. Finally, with evidence for substantial sex differences in hypertension that are preserved across species,⁴¹ it will be important to study cognitive effects of salt in female rodents, since existing research has focused exclusively on males.

Additional research in younger human populations will also be important, given that most studies to date have focused on older age groups, and following evidence from rodent studies that the detrimental effects of salt are more pronounced in older than younger animals.²⁹ A final target for future research is to continue to refine methods of estimating salt intake, given that self-report measures yield substantially lower estimates than 24-h urine collection methods,^{20,42} which are also not well matched to one-off 'spot' urine assessments.⁴³

Salt within the obesogenic environment - recommendations

Nonetheless, this new evidence reinforces the need to direct attention to the health risks of excessive salt consumption. Given evidence indicating that individuals who are informed about the potential health risks of salt are less likely to consume excessive amounts,⁴⁴ the efficacy of public awareness campaigns might be improved by highlighting that excess salt consumption may adversely affect cognitive as well as cardiovascular function. Industry involvement will also be key, given that three-quarters of sodium intake in Europe and North America is estimated to be derived from processed foods.⁴⁵ Modelling studies using American data have estimated that 44,000-92,000 deaths from cardiovascular disease could be prevented by reducing population-wide salt intake by 3 g/day.⁴⁶

We argue that changes to food systems should adopt a multi-pronged approach targeting ultra-processed or 'discretionary' foods that are highly palatable and advertised relentlessly in modern food environments.⁴⁷ In addition to the potential adverse effects on health over the longer term, salt also influences food intake acutely by enhancing palatability. Yet these effects are complex: An early study in primates showed that the firing rate of neurons in the amygdala in response to the sight of preferred foods (e.g. watermelon) was blunted when the foods were salted.⁴⁸ Foods in modern environments are high not only in salt, but saturated fat and sugars, with ample evidence that high consumption of these macronutrients also compromises cognitive function. Work by our own, and other groups has shown that consumption of diets high in fat and sugar can impair performance in hippocampal-dependent spatial memory tasks,^{49,50} supported by emerging human data showing that acute consumption of diets high in saturated fat and refined carbohydrates leads to impairments in cognitive function⁵¹ and produces structural brain changes.⁵² As shown for salt, the cognitive effects of fat and sugar appear to relate to hippocampal inflammation and oxidative stress,⁵³ but also to increased leakiness of the blood-brain barrier⁵⁴ and changes in the composition of the bacteria that inhabit our gut.⁵⁵ Therefore, it will be important to test how the effects of salt interact with or exacerbate those produced by high-fat, high-sugar diets on cognition, the gut microbiome and the brain.

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AUTHOR DISCLOSURE

REFERENCES

1. Land MA, Neal BC, Johnson C, Nowson CA, Margerison C, Petersen KS. Salt consumption by Australian adults: a systematic review and meta-analysis. *Med J Aust.* 2018;208:75-81.
2. Hipgrave DB, Chang S, Li X, Wu Y. Salt and sodium intake in China. *JAMA.* 2016;315:703-5.
3. Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M et al. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). *Hypertens Res.* 2009;32:3-107.
4. Johnson C, Praveen D, Pope A, Raj TS, Pillai RN, Land MA, Neal B. Mean population salt consumption in India: a systematic review. *J Hypertens.* 2017;35:3-9.
5. Cordain L, Eaton SB, Sebastian A, Mann N, Lindeberg S, Watkins BA, O'Keefe JH, Brand-Miller J. Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr.* 2005;81:341-54.
6. Grimes CA, Riddell LJ, Campbell KJ, Beckford K, Baxter JR, He FJ, Nowson CA. Dietary intake and sources of sodium and potassium among Australian schoolchildren: results from the cross-sectional Salt and Other Nutrients in Children (SONIC) study. *BMJ Open.* 2017;7:e016639.
7. Trieu K, Neal B, Hawkes C, Dunford E, Campbell N, Rodriguez-Fernandez R et al. Salt Reduction Initiatives around the World - A Systematic Review of Progress towards the Global Target. *PLoS One.* 2015;10:e0130247.
8. Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ.* 2009;339:b4567.
9. Mozaffarian D, Fahimi S, Singh GM, Micha R, Khatibzadeh S, Engell RE et al. Global sodium consumption and death from cardiovascular causes. *N Engl J Med.* 2014;371:624-34.
10. Mente A, O'Donnell M, Rangarajan S, McQueen M, Dagenais G, Wielgosz A et al. Urinary sodium excretion, blood pressure, cardiovascular disease, and mortality: a community-level prospective epidemiological cohort study. *Lancet.* 2018;392:496-506.
11. Messerli FH, Hofstetter L, Bangalore S. Salt and heart disease: a second round of "bad science"? *Lancet.* 2018;392:456-8.
12. He FJ, MacGregor GA. Effect of longer-term modest salt reduction on blood pressure. *Cochrane Database Syst Rev.* 2004:CD004937.
13. Heye AK, Thrippleton MJ, Chappell FM, Hernandez Mdel C, Armitage PA, Makin SD et al. Blood pressure and sodium: Association with MRI markers in cerebral small vessel disease. *J Cereb Blood Flow Metab.* 2016;36:264-74.
14. Hucke S, Wiendl H, Klotz L. Implications of dietary salt intake for multiple sclerosis pathogenesis. *Mult Scler.* 2016;22:133-9.
15. Wilck N, Matus MG, Kearney SM, Olesen SW, Forslund K, Bartolomeaus H et al. Salt-responsive gut commensal modulates TH17 axis and disease. *Nature.* 2017;551:585-9.

16. Lanaspá MA, Kuwabara M, Andres-Hernando A, Li N, Cicerchi C, Jensen T et al. High salt intake causes leptin resistance and obesity in mice by stimulating endogenous fructose production and metabolism. *Proc Natl Acad Sci U S A*. 2018;115:3138-43.
17. Fiocco AJ, Shatenstein B, Ferland G, Payette H, Belleville S, Kergoat MJ, Morais JA, Greenwood CE. Sodium intake and physical activity impact cognitive maintenance in older adults: the NuAge Study. *Neurobiol Aging*. 2012;33:829 e21-8.
18. Salerno-Kennedy R, & Cashman, K. D. The relationship between nutrient intake and cognitive performance in people at risk of dementia. *Irish journal of medical science*. 2007;176:193-8.
19. Nowak KL, Fried L, Jovanovich A, Ix J, Yaffe K, You Z, Chonchol M. Dietary sodium/potassium intake does not affect cognitive function or brain imaging indices. *Am Jof Nephrol*. 2018;47:57-65.
20. Haring B, Wu C, Coker LH, Seth A, Snetselaar L, Manson JE, Rossouw JE, Wassertheil-Smoller S. Hypertension, dietary sodium, and cognitive decline: results from the Women's Health Initiative Memory Study. *Am J Hypertens*. 2016;29:202-16.
21. Rush TM, Kritiz-Silverstein D, Laughlin GA, Fung TT, Barrett-Connor E, McEvoy LK. Association between dietary sodium intake and cognitive function in older adults. *J Nutr Health Aging*. 2017;21:276-83.
22. Afsar B. The relationship between cognitive function, depressive behaviour and sleep quality with 24-h urinary sodium excretion in patients with essential hypertension. *High Blood Press Cardiovasc Prev*. 2013;20:19-24.
23. Rondanelli M, Solerte SB, Ferrari E. Electrolytes and cognitive function in the elderly: relationship between serum sodium and chloride concentrations and psychometric test scores. *Panminerva Med*. 1998;40:191-5.
24. Murtaugh MA, Beasley JM, Appel LJ, Guenther PM, McFadden M, Greene T, Tooze JA. Relationship of sodium intake and blood pressure varies with energy intake: secondary analysis of the DASH (Dietary Approaches to Stop Hypertension)-Sodium Trial. *Hypertension*. 2018;71:858-65.
25. Morris MJ, Beilharz JE, Maniam J, Reichelt AC, Westbrook RF. Why is obesity such a problem in the 21st century? The intersection of palatable food, cues and reward pathways, stress, and cognition. *Neurosci Biobehav Rev*. 2015;58:36-45.
26. Liu YZ, Chen JK, Li ZP, Zhao T, Ni M, Li DJ, Jiang CL, Shen FM. High-salt diet enhances hippocampal oxidative stress and cognitive impairment in mice. *Neurobiol Learn Mem*. 2014;114:10-5.
27. Ge Q, Wang Z, Wu Y, Huo Q, Qian Z, Tian Z, Ren W, Zhang X, Han J. High salt diet impairs memory-related synaptic plasticity via increased oxidative stress and suppressed synaptic protein expression. *Mol Nutr Food Res*. 2017;61.
28. Guo CP, Wei Z, Huang F, Qin M, Li X, Wang YM et al. High salt induced hypertension leads to cognitive defect. *Oncotarget*. 2017;8:95780-90.
29. Chugh G, Asghar M, Patki G, Bohat R, Jafri F, Allam F et al. A high-salt diet further impairs age-associated declines in cognitive, behavioral, and cardiovascular functions in male Fischer brown Norway rats. *J Nutr*. 2013;143:1406-13.

30. Faraco G, Brea D, Garcia-Bonilla L, Wang G, Racchumi G, Chang H et al. Dietary salt promotes neurovascular and cognitive dysfunction through a gut-initiated TH17 response. *Nat Neurosci.* 2018;21:240-9.
31. Craft S. The role of metabolic disorders in Alzheimer disease and vascular dementia: two roads converged. *Arch Neurol.* 2009;66:300-5.
32. Dahl LK, Heine M, Tassinari L. Role of genetic factors in susceptibility to experimental hypertension due to chronic excess salt ingestion. *Nature.* 1962;194:480-2.
33. Rapp JP. Dahl salt-susceptible and salt-resistant rats. A review. *Hypertension.* 1982;4:753-63.
34. Terry AV, Jr., Hernandez CM, Buccafusco JJ. Dahl salt-sensitive and salt-resistant rats: examination of learning and memory performance, blood pressure, and the expression of central nicotinic acetylcholine receptors. *Neuroscience.* 2001;103:351-63.
35. Ruiz-Opazo N, Lopez LV, Tonkiss J. Modulation of learning and memory in Dahl rats by dietary salt restriction. *Hypertension.* 2004;43:797-802.
36. Oparil S. Low sodium intake--cardiovascular health benefit or risk? *N Engl J Med.* 2014;371:677-9.
37. Hurley SW, Johnson AK. The biopsychology of salt hunger and sodium deficiency. *Pflugers Arch.* 2015;467:445-56.
38. Martus W, Kim D, Garvin JL, Beierwaltes WH. Commercial rodent diets contain more sodium than rats need. *Am J Physiol Renal Physiol.* 2005;288:F428-31.
39. Velkoska E, Cole TJ, Morris MJ. Early dietary intervention: long-term effects on blood pressure, brain neuropeptide Y, and adiposity markers. *Am J Physiol Endocrinol Metab.* 2005;288:E1236-43.
40. Smith E, Hay P, Campbell L, Trollor JN. A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. *Obes Rev.* 2011;12:740-55.
41. Sandberg K, Ji H. Sex differences in primary hypertension. *Biol Sex Differ.* 2012;3:7.
42. Santos JA, Webster J, Land MA, Flood V, Chalmers J, Woodward M, Neal B, Petersen KS. Dietary salt intake in the Australian population. *Public Health Nutr.* 2017;20:1887-94.
43. Zhou L, Tian Y, Fu JJ, Jiang YY, Bai YM, Zhang ZH, et al. Validation of spot urine in predicting 24-h sodium excretion at the individual level. *Am J Clin Nutr.* 2017;105:1291-6.
44. Li TQ, Y.; Lou, P.; Chang, G.; Chen, P.; Qiao, C.; Zhang, P.; & Zhang, N. Salt Intake and Knowledge of Salt Intake in a Chinese Population: A Cross-sectional Study. *Internal Medicine.* 2015;5:186.
45. Brown IJ, Tzoulaki I, Candeias V, Elliott P. Salt intakes around the world: implications for public health. *Int J Epidemiol.* 2009;38:791-813.
46. Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ, Goldman L. Projected effect of dietary salt reductions on future cardiovascular disease. *N Engl J Med.* 2010;362:590-9.
47. Hall KD. Did the Food Environment Cause the Obesity Epidemic? *Obesity.* 2018;26:11-3.
48. Nishijo H, Ono T. Food memory: neuronal involvement in food recognition. *Asia Pac J Clin Nutr.* 1992;1:3-12.

49. Beilharz JE, Maniam J, Morris MJ. Short exposure to a diet rich in both fat and sugar or sugar alone impairs place, but not object recognition memory in rats. *Brain Behav Immun*. 2014;37:134-41.
50. Kendig MD. Cognitive and behavioural effects of sugar consumption in rodents. A review. *Appetite*. 2014;80:41-54.
51. Attuquayefio T, Stevenson RJ, Oaten MJ, Francis HM. A four-day Western-style dietary intervention causes reductions in hippocampal-dependent learning and memory and interoceptive sensitivity. *PLoS One*. 2017;12:e0172645.
52. Stranahan AM, Norman ED, Lee K, Cutler RG, Telljohann RS, Egan JM, Mattson MP. Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats. *Hippocampus*. 2008;18:1085-8.
53. Beilharz JE, Maniam J, Morris MJ. Short-term exposure to a diet high in fat and sugar, or liquid sugar, selectively impairs hippocampal-dependent memory, with differential impacts on inflammation. *Behav Brain Res*. 2016;306:1-7.
54. Kanoski SE, Zhang Y, Zheng W, Davidson TL. The effects of a high-energy diet on hippocampal function and blood-brain barrier integrity in the rat. *J Alzheimers Dis*. 2010;21:207-19.
55. Beilharz JE, Kaakoush NO, Maniam J, Morris MJ. Cafeteria diet and probiotic therapy: cross talk among memory, neuroplasticity, serotonin receptors and gut microbiota in the rat. *Mol Psychiatry*. 2018;23:351-61.

Table 1. Summary of recent studies in humans investigating the effects of dietary salt on cognition

| Study | Study design/ participants | Salt intake estimated via: | Cognitive task and result | Association with blood pressure |
|------------------------------------------------|-----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| Haring et al. (2016) ²⁰ | Prospective follow-up study (mean follow-up: 9.1 years) of 6,426 women aged 65-69 | Food frequency questionnaire (past 3 months): compared with 24-h urinary excretion in subset of ppts | Modified Mini Mental State Examination (3MS): no association between high sodium intake (> 1.5g/day), mild cognitive impairment (<10 th percentile on 1+ cognitive domain) or probable dementia in women with hypertension or taking antihypertensive medication | Higher self-reported sodium intake in hypertensive vs. normotensive women |
| Fiocco et al. (2012) ¹⁷ | 3-year longitudinal study of 1262 adults aged 67-84 | Food frequency questionnaire (past year) | Mini Mental State Examination (MMSE): Higher self-reported salt intake associated with lower scores, but only in participants reporting low exercise levels | No significant difference in % hypertensives across sodium intake tertiles |
| Nowak et al. (2018) ¹⁹ | Prospective follow-up study (mean follow-up: 6.9 years) of 1,194 adults aged 74 ± 3 | Food frequency questionnaire | Modified Mini Mental State Examination (3MS): No association between sodium intake and increased risk of cognitive decline (≥1.5 SD of average decline) or structural brain measures, as assessed by MRI However, the odds of cognitive decline were associated with sodium:potassium intake | No differences in systolic BP, diastolic BP or % hypertension between quartiles of sodium intake |
| Afsar (2013) ²² | Cross-sectional study of 119 adults (mean age 54 ± 16) with hypertension | 24-h urine collection | Standardised Mini Mental State Examination (SMMSE): higher sodium excretion associated with poorer performance Pittsburgh Sleep Quality Index: not associated with sodium excretion Beck Depression Inventory: not associated with sodium excretion | Sodium excretion positively associated with both systolic and diastolic blood pressure |
| Rush et al. (2017) ²¹ | Cross-sectional study of 925 adults aged 50-97 | Food frequency questionnaire (past month) | Mini Mental State Examination (MMSE): lower self-reported salt intake associated with poorer MMSE scores Trails-B task (executive function/visuomotor capacity): lower salt intake weakly associated with poorer performance (more time taken to complete) Verbal fluency test: No association between salt intake and fluency (# animals spontaneously named in 1-min) | Highest % of hypertension in 1 st and 4 th quartiles of sodium intake (chi-square test) |
| Rondanelli et al. (1998) ²³ | Cross-sectional study of 82 older adults (mean age 87 ± 6) | Serum sodium | Mini Mental State Examination (MMSE): higher serum sodium associated with lower MMSE scores. Cognitive performance also correlated negatively with serum chloride, but not with other nutritional measures (e.g. triglycerides or total cholesterol) | Not assessed |
| Salerno-Kennedy & Cashman (2007) ¹⁸ | Observational study of 44 blood relatives of Alzheimer's Disease patients (mean age 57) | Food frequency questionnaire (past week) | Mini Mental State Examination (MMSE): Participants with lowest MMSE scores (n=4) reported higher salt intakes than the remaining cohort (n=40). Note small sample size may limit interpretation | Not assessed |

Table 2. Summary of recent studies in rodents investigating the effects of dietary salt on cognition

| Study | Animal model | Salt diet (provided in chow) | Cognitive test and result | Blood pressure outcome (method) | Body weight outcome |
|--------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| Faraco et al. (2018) ³⁰ | Young adult (8 weeks old) or aged (12 to 13-month-old) male C57BL/6 mice | 0.5% (control), 4% or 8% NaCl diet for 12 weeks (no significant difference in consumption) | Novel object recognition (short-term memory): both aged and young mice impaired after 8 and 12 weeks on 8% NaCl diet. On 4% NaCl diet impairment in both ages after 12 weeks Barnes maze (spatial learning and memory): no effect of high-salt diets on acquisition (spatial learning). Mice fed high-salt diet were impaired when escape hole location was moved (higher latency to reach, more distance travelled) Nesting behaviour: impaired after 12 weeks of high-salt diet (more untorn nesting, lower nest score) | No differences in systolic BP or MAP over 12 weeks of diet (tail cuff plethysmography) | No significant difference in body weight gain |
| Liu et al. (2014) ²⁶ | Adult male C57BL/6 mice | 0.4% or 7% NaCl diet for 12 weeks | Morris water maze (spatial learning and memory): high-salt diet impaired memory (lower % time and # entries in target quadrant during test phase) | No differences in systolic or diastolic BP after 12 weeks of diets (cannulation of right internal carotid artery) | No significant difference in body weight gain |
| Ge, Wang et al. (2017) ²⁷ | Adult male C57BL/6J mice | 0.4% or 8% NaCl diet for 4 or 7 weeks (high-salt diet increased food intake) | Open field test (anxiety): no effect of high-salt diet Place recognition task (spatial memory): high-salt diet feeding for 7, but not 4 weeks, impaired place recognition. Fear conditioning (long-term memory): high-salt diet feeding for 4 or 7 weeks impaired memory (reduced freezing in a context paired with foot-shock) | No difference in MAP between groups after 4 or 7 weeks (tail cuff plethysmography) | High-salt diet significantly reduced body weight gain |
| Chugh et al. (2013) ²⁹ | Male adult (2-month old) or aged (20-month old) Fischer Brown Norway rats | 0.4% or 8% NaCl diet for 4 weeks (no significant difference in consumption) | Open field test (anxiety): high-salt diet increased anxiety (decreased time in lit area of box) in aged rats; no effect in younger adult rats Light-dark test (anxiety): aged rats were more anxious (less time in centre) with no effect of dietary salt Radial arm water maze (learning and memory): high-salt diet impaired memory (more errors in test phase) in aged rats; no effect in young adult rats | High-salt diet increased systolic BP in aged but not young adult rats after 4 weeks of diet (radio telemetry probe). Age increased systolic but not diastolic BP | No significant difference in body weight gain |
| Guo et al. (2017) ²⁸ | Adult male (2-month old) Sprague-Dawley rats | 0.26% or 8% NaCl diet for 9 weeks (consumption not reported) | Open field test (anxiety): no effect of high-salt diet. Fear conditioning (long-term memory): high-salt diet impaired fear memory (reduced freezing in a context paired with foot shock) Morris water maze (spatial learning and memory): high-salt diet impaired spatial memory during probe trial (lower number of platform crossing) but not spatial learning (latency to escape in acquisition) | High-salt diet increased systolic BP from 3 weeks of diet onwards (tail cuff plethysmography) | No significant difference in body weight gain |

Table 2. Summary of recent studies in rodents investigating the effects of dietary salt on cognition (cont.)

| Study | Animal model | Salt diet (provided in chow) | Cognitive test and result | Blood pressure outcome (method) | Body weight outcome |
|----------------------------------------|--------------------------------------------------------|--------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| Salt-sensitive strains | | | | | |
| Ruiz-Opazo et al. (2004) ³⁵ | Adult male salt-sensitive and salt-resistant Dahl rats | 0.4% (regular salt) or 0.008% (low-salt) NaCl diet for 16 weeks (consumption not reported) | <p>Morris water maze (spatial learning and memory): no effect of strain or of regular vs. low-salt diet on spatial learning (latency to escape during acquisition). On regular salt diet, no differences in spatial memory between sensitive and resistant strains. Performance by salt-resistant rats was improved when fed a low-salt versus regular salt diet (more platform crossings and search time in correct quadrant during probe trial)</p> <p>Social recognition task (social memory): on regular salt diet, social recognition memory (reduced investigation of a novel rat on second exposure) intact in both strains. On a low salt diet, social recognition memory impaired in salt-sensitive strain (no decline in exploration)</p> <p>Social transmission of food preference (hippocampal-dependent memory): on regular salt diet, both strains preferred to eat a food flavoured with a 'trained' odour pre-exposed by rubbing on another rat. On a low salt diet, salt-sensitive rats showed no preference for the trained odour</p> <p>Novel object recognition (short-term memory): no effect of low-salt diet in salt-sensitive or salt-resistant rats</p> | No group differences in systolic blood pressure after 10 weeks of diet (tail cuff measurement) | No significant differences in body weight gain |
| Terry Jr. et al. (2001) ³⁴ | Adult male salt-sensitive or salt-resistant Dahl rats | 8% sodium diet or standard Purina Rodent chow (consumption not reported) | <p>Passive avoidance testing (inhibitory learning): no effect of strain (resistant or sensitive) or diet (high salt vs. standard chow) on latency to enter the shock-paired compartment</p> <p>Radial arm maze (working memory): impairment in salt-sensitive vs. resistant strain (fewer entries into food-baited maze arms), regardless of diet</p> <p>Morris water maze (spatial learning and memory): salt-sensitive rats fed a high-salt diet showed impaired spatial learning (slower to locate the platform during training trials) and memory (less time searching in target quadrant) during test</p> | Systolic and diastolic BP were higher in salt-sensitive than salt-resistant rats, and highest in salt-sensitive rats fed high-salt diet (tail cuff measures and ileac artery catheterisation) after 6 weeks on diets | Not reported |

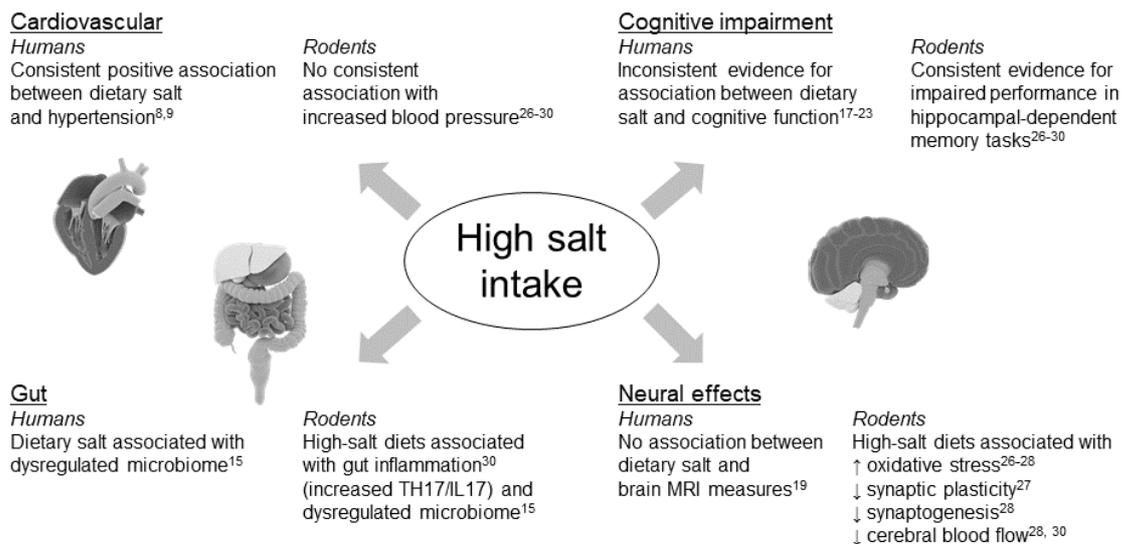


Figure 1. Overview of evidence for adverse effects of salt intake on cognition and other health outcomes. Note: while this review focuses on the effects of high intake over the long term, there is also evidence for cognitive impairment following acute salt depletion³⁷.