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REVIEW

Neuroimaging, neuromodulation, and population health: the neuroscience of chronic disease prevention

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Preventable chronic diseases are the leading cause of death in the majority of countries throughout the world, and this trend will continue for the foreseeable future. The potential to offset the social, economic, and personal burdens associated with such conditions depends on our ability to influence people's thought processes, decisions, and behaviors, all of which can be understood with reference to the brain itself. Within the health neuroscience framework, the brain can be viewed as a predictor, mediator, moderator, or outcome in relation to health-related phenomena. This review explores examples of each of these, with specific reference to the primary prevention (i.e., prevention of initial onset) of chronic diseases. Within the topic of primary prevention, we touch on several cross-cutting themes (persuasive communications, delay discounting of rewards, and self-control), and place a special focus on obesity as a disorder influenced by both eating behavior and exercise habits.

Keywords: brain; neuroscience; prevention; disease; communication; behavior; prevention neuroscience

Introduction

Chronic illnesses such as diabetes, cancer, and cardiovascular disease have long been the primary limiting factors for the human lifespan, and will remain so for the foreseeable future.[1] This state of affairs does not apply selectively to first-world countries: with escalating rates of smoking and obesity, the devastating effects of chronic disease may be felt at an even higher level in second- and third-world countries than currently the case in first-world countries.[2] Rather than replacing other prevalent threats to life such as malnutrition and infectious disease, chronic illness will (perhaps paradoxically) exist alongside these, among populations that lack the resources for management of these conditions after they surface.[1] For this reason, primary prevention—that is, prevention of initial onset—of chronic illness is truly a world-wide concern, and never before has there been such a need for the scientific community to inform such efforts.

Primary prevention research has traditionally been approached from the perspective of environmental, societal, and behavioral determinants of health outcomes.[3] As such, the internal workings of the brain have been previously seen as the purview of other areas of research, or for those scientists who are interested in the brain only as a biological outcome variable. This is rapidly changing, to the extent that disease prevention—as an area of scientific inquiry—is expanding to harness concepts, methods, and findings from several subfields of neuroscience.[4–7]

This review will explore several areas of empirical research that illustrate the potential scope of health neuroscience in the context of primary disease prevention. In accordance with the health neuroscience perspective, examples will be presented wherein the brain serves as a predictor, a mediator, a moderator, and (more conventionally) an outcome. This review begins with several cross-cutting concepts that are of wide applicability in disease

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prevention (i.e., decision making, self-control, and delay discounting), and then moves to several specific behaviors that are particularly relevant to the development of excess body weight and obesity.

Cross-cutting concepts in disease prevention

Research in the past two decades within neuroeconomics and social neuroscience has highlighted core neural processes implicated in a general class of decision making, of which health-related decisions are a subset. By combining cognitive neuroscience perspectives with behavioral economics, neuroeconomics examines the neural correlates of economic behavior,[8] and social neuroscience[9,10] incorporates perspectives about self-related and social influences developed in social psychology to the field of cognitive neuroscience. One perspective from this body of research is that a common valuation system integrates multiple sources of information to calculate a common value signal or common currency that allows for comparison of decision alternatives that may not otherwise be comparable (e.g., would you rather have an apple or an orange? Watch television or exercise?).[11] The supporting brain systems are composed of different structures, with the reward value system being primarily composed of the ventral tegmental areas, dorsal and ventral striatum, as well as some parts of the prefrontal cortex (PFC) (e.g., orbitofrontal cortex (OFC)). The lateral portions of the PFC as well as the anterior cingulate cortex support human executive functions; such functions help implement decision making as overt behavior.[12–16] The functional interaction of these two systems provides important regulatory control over behavior,[17–19] and along with brain systems implicated in social cognition and other key decision variables, informs a wide range of decision processes, including persuasion,[20] self-control,[21 c.f. 22] and delay discounting.[23] Given the relevance of reward and positive valuation across other processes that are critical to health decision making, we provide a brief overview here, followed by examples of more specific processes relevant to disease prevention.

How does the human brain represent the hedonic value of different temptations and decision alternatives? Functional neuroimaging research has shown that consumption of appetitive foods[24,25] as well as exposure to food and other hedonic cues such as drugs and money all lead to increased activity in the ventral striatum and aspects of ventromedial prefrontal cortex (vmPFC) and OFC.[26–30] Moreover, studies show that the response in these regions is associated with reward receipt and tracks momentary changes in the hedonic pleasure, as in the case of one study where participants consumed chocolate to satiety.[31] Below, we review pathways to altering this signal, including social influence and persuasive communications, changing the weight of inputs to the value calculation through self-regulation, and by changing focus on present versus future rewards through delay discounting. Together, the literature highlights the ways that a core set of neurocognitive functions may be relevant across a wide range of processes involved in disease prevention. Homing in on these functions may provide more efficient pathways to intervention.

Persuasive communications

The leading causes of morbidity and mortality stem from behaviors that people can change.[32] Critically, these behaviors do not occur in a vacuum and can be socially influenced by media messages,[33] interpersonal communication,[34,35] and social norms.[36] Consistent with expectancy-value models of behavior change,[37] recent theory suggests that reward valuation (of ideas and messages) is key in determining whether people decide to share information with others and whether receivers are persuaded.[20,37,38] As described above, computing value involves brain activity within regions including the vmPFC (Fig. 1) and ventral striatum.[11,30,39–41] Activity within this system can be altered by normative influence from peers.[42–47] For example, in a study of food preferences, neural activity in ventral striatum was greater when participants' food preferences were consistent with (experimentally manipulated) peer feedback, which the authors suggest may reflect reward value associated with being in line with peers. Later, when providing a second set of ratings about the same foods, foods earlier rated more highly by peers elicited greater activity in the value system within the vmPFC.[45]

Activity in the medial PFC (mPFC)[48–52] and other brain responses[53,54] also predict the effectiveness of persuasive health messages encouraging behavior change. For example, brain activity in the mPFC in response to messages encouraging people to quit smoking,[48,55,56] wear more sunscreen,[51,57] and get

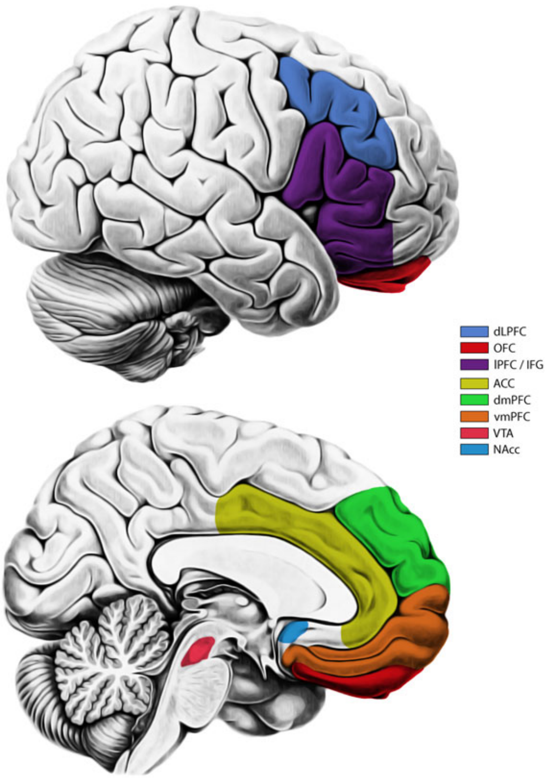

Figure 1. Anatomical regions of the brain involved in health communication and behavioral processes pertaining to disease prevention. dLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; lPFC, lateral prefrontal cortex; IFG, inferior frontal gyrus; ACC, anterior cingulate cortex; dmPFC, dorsal medial prefrontal cortex; vmPFC, ventromedial prefrontal cortex, VTA, ventral tegmental area; NAcc, nucleus accumben.

more physical exercise[49] has been associated with message-consistent behavior change. This brain activity is associated with behavior change above and beyond several different self-report predictors of behavior change (for a review, see Ref. 20). By contrast, the perceived effectiveness of messaging at scale is associated within the middle frontal and superior temporal gyri,[54] further emphasizing that the antecedents of self-report outcomes may differ from those of behavioral outcomes.

Activity in this same value system that is associated with health behavior change also plays a central role in people's decisions to share health information with others.[58–60] Finally, brain activity in overlapping regions of the value system in relatively small groups of individuals has also been associated with larger scale health-relevant behaviors such as population-level responses to antismoking campaigns[50,61] and sharing of health news.[60]

More recent research has moved beyond the exclusive use of average activity within single brain regions and taken greater advantage of the temporal dynamics that occur across the course of message receipt. One line of research demonstrates that connectivity between parts of the value system, including the vmPFC and ventral striatum during exposure to health messages, is associated with greater message-consistent behavior change in physical activity[62] and smoking domains[62] and explained additional variance in message-consistent behavior change beyond univariate activity alone. This highlights the value of considering not only average activity in response to health messages, but also more dynamic connectivity relationships. Conceptually, this also bolsters confidence in the idea that the vmPFC is tracking how valuable the health information is to the person and how likely they are to act accordingly in the future.

This common value account of persuasion and behavior change also aligns with the idea that a wide range of message-framing strategies, including fear appeals highlighting potential negative outcomes, gain versus loss framing, prevention versus promotion focus, and framing messages in individual versus collective terms, can be unified as a consequence-based argument;[63] in other words, each of these strategies highlights particular risks or benefits to the actor, which feed into a calculation of the consequences (i.e., potential value) of different courses of action.[63]

What are the key ingredients contributing to the value calculation? Two key properties of messages that may impact their success include self-relevance and social relevance. Several theories of health behavior change highlight these elements[37,63–65] and recent evidence also implicates brain systems that code for self and social relevance in receptivity to messaging (for a review, see Ref. 20). Consistent with the view that finding value in messages is one key ingredient to success, building on insights from self-affirmation theory, participants who were first randomized to reflect on their most important core values (versus participants who reflected on unimportant values to them) went on to show greater activity in the vmPFC during health messages, which, in turn, produced greater message-consistent behavior change.[20,49] Likewise, participants whose vmPFC activity more strongly represented the negative (risk) consequences of smoking during exposure to graphic warning labels were also more likely to reduce their smoking behavior.[20,49,66] Taking a different approach, Chua and colleagues demonstrated that tailoring message content to smokers increased activity in the mPFC, which also predicted message-consistent behavior change.[48] All of these studies are consistent with the idea that finding personal relevance in messages may be one key factor in determining message value, and subsequent behavior change. In parallel, both behavioral and neural evidence point to the importance of social norms in influencing the value calculation as well.[58]

Self-control

Many human behaviors that generate disease risk are characterized by a tendency to choose immediate over delayed rewards, and inability to consistently resist the things that are pleasurable in favor of those that are ultimately good for us. For example, overindulgence in appetitive foods, screen time, substance abuse, and other hedonic pursuits tend to crowd out behaviors that have better health-related outcomes in the long run. Essentially, many of these tendencies can be characterized as problems of self-control.[12]

There have been many developments in how behavioral scientists conceptualize self-control over the past few decades, with some of the more important insights gained from cross-pollination among the fields of neuroscience, social psychology, and behavioral economics. For instance, there have been substantial leaps in our ability to map brain systems onto the generation of hedonic responses, representation of nonimmediate outcomes, and the negotiation of conflict between these.[18,21,67–69] One concept tying all of these concepts together is self-regulation, which broadly refers to the capacity to actively manage thoughts, cravings, or emotions in order to pursue future-oriented goals.[12] Using a variety of neuroimaging methods, neuroscientists have examined how the structure, function, and connectivity of different brain regions are involved in representing the strength of hedonic responses and the ability to regulate them.[12,70] Much of this work focuses on distinct brain systems involved in representing the reward or motivational value of a stimulus as well as executive functions (e.g., planning, response inhibition, working memory, and decision making). Some recent theories have framed these forces as competing, whereas other theories posit different inputs to a general form of value-based decision making referenced in the prior section.[21] Yet, these disparate approaches agree on the fact that the value system and portions of lateral PFC come together to inform a broad class of (health-relevant) decisions.

In the laboratory context, one of the most common methods of eliciting a hedonic response is to present individuals with cues that are associated with a reward (e.g., visual imagery and scents). For instance, humans will show physiological signs of craving, such as increased heart rate and salivary responses, when exposed to food cues,[71] just as smokers respond similarly when exposed to cigarette cues.[72] These hedonic cues capture attention[73–75] and increase craving and consumption for the desired items,[76] with corresponding activity in the brain's reward valuation system. The research outlined above focuses primarily on the passive viewing of food or drug cues as a means of identifying regions involved in representing hedonic value. Here, we now turn to those brain systems involved in regulating these responses. Over the last decade, a number of studies have converged on the lateral PFC as being important for processes relevant to self-regulation, such as response inhibition[77] and cognitive reappraisal.[78,79] Research has shown increased activation in this region when individuals attempt to regulate their responses to appetitive food cues,[80–83] drug cues,[84,85] monetary rewards,[86] and motivationally relevant facial expressions.[87] Moreover, this increased activation during self-regulation is often associated with a concomitant decrease in activity in those regions involved in representing hedonic value. Interestingly, temporary inactivation of the lateral PFC (Fig. 1) using transcranial magnetic stimulation has been shown to disrupt some aspects of intentional control that may be central to understanding addictions, and risk taking more generally.[88]

More broadly, in recent years, there has been a trend toward using neuroscientific data and findings to predict future self-regulation successes and failures using a "brain-as-predictor" approach.[89,90] Common across much of this new work is the use of functional or structural measures of brain activity in the reward system and prefrontal regions implicated in self-control to predict health outcomes such as smoking cessation, dieting success, drinking, and obesity.[69] For example, individual differences in striatal and OFC activation by appetitive food cues have been shown to be associated with body mass index[91] and, in a longitudinal study, to prospectively predict weight gain during the first year of college (e.g., the "freshman fifteen") in adults,[92] with similar findings being shown in adolescents.[93] Along similar lines, activity in the OFC in response to alcohol cues has also been associated with frequency of drinking among college students.[94] Recent work has sought to use novel experience-sampling methods that rely on smart phone technology to follow individuals throughout the day in order to relate their daily experiences of self-control success and failure back to neural measures of hedonic value and response inhibition. In one of the first studies of this kind, Berkman and colleagues followed smokers attempting to quit smoking over a 3-week period and found that activity in the lateral PFC during a response inhibition task prospectively predicted those smokers who demonstrated reduced craving and consumption over the study period.[95] Similarly, in the domain of eating, it was shown that both neural responses during a similar response inhibition task as well as hedonic neural response to food cues prospectively predicted difficulty regulating food desires, as well as the overall strength of the daily food desires, when measured by experience sampling.[82] More recently, Lopez and colleagues extended these findings in a sample of dieters, demonstrating that greater recruitment of the lateral PFC during food cue exposure was prospectively associated with real-world dieting success measured during a week of experience sampling.[96] Although much of this work is still new and focuses more on uncovering associations between brain and behavior rather than building truly predictive models (i.e., out-of-sample prediction), these studies nevertheless represent an exciting new avenue of research that suggests potential "neuromarkers" that may be used to predict future health outcomes (Fig. 2).[90,97]

Delay discounting

The need for self-control is arguably greatest under conditions where one must decide between two alternatives, one of which delivers a small but immediate reward, while the other carries a larger later reward. Pursuit of concrete near-term rewards at the expense of delayed but ultimately more valuable rewards (relationships and lifespan) is the crux of many self-defeating behavioral tendencies in the health domain. The phenomenon of delay-discounting (i.e., decrease in the value of a reward as a function of the delay to receipt of that reward) therefore identifies a prototype for situations wherein self-control is necessary for the realization of positive health outcomes.

McClure and colleagues[23] used functional magnetic resonance imaging (fMRI) to examine the

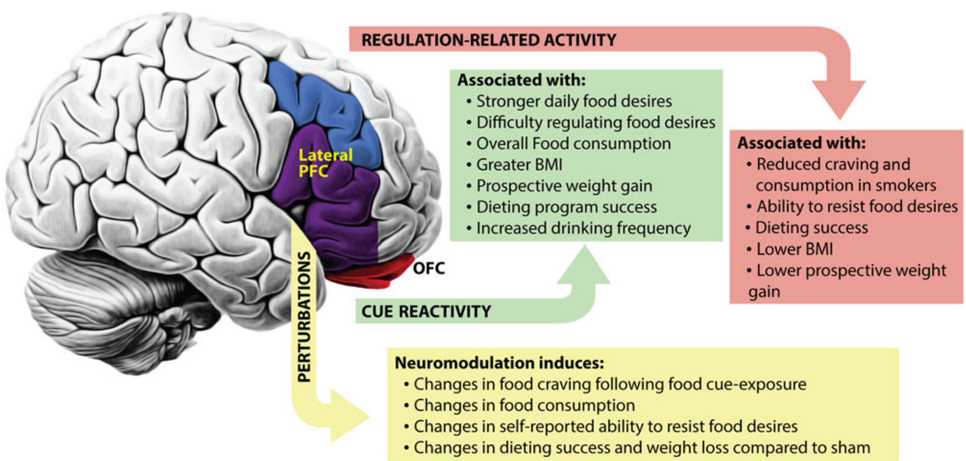

Figure 2. Illustration of findings from studies using a "brain-as-predictor" approach revealing independent associations between reward cue-related activity (green box) or regulation-related activity (response inhibition, reappraisal; red box) and real-world health outcomes in the domains of smoking, eating, and drinking. Noninvasive brain stimulation interventions designed to excite activity in the lateral PFC have been associated with positive dietary health outcomes (yellow box).

neural correlates of delay discounting in healthy adults and reported relatively greater activity of the limbic and paralimbic brain regions when participants chose the immediately available options. In contrast, relatively greater activity in areas of the PFCs was detected when the delayed options were selected.[23] Neuroeconomic and related studies have further implicated the dorsolateral PFC (dlPFC), posterior parietal cortex, anterior cingulate cortex, and anterior insular cortex in alcohol use disorder and other addictions.[98–101] Indeed, delay discounting has been proposed as a candidate behavioral marker for the entire addiction process.[102] Another related measure is demand (the sensitivity of consumption to price). To date, however, only one study has examined the neural correlates of drug demand.[102] When making and considering purchases of alcoholic drinks, the activated neural regions included the limbic and paralimbic regions (e.g., ventral striatum and insula), regions associated with cognitive control (e.g., dlPFC), and those associated with mental computation (e.g., angular gyrus). Similar results have been observed with neuroimaging studies of marijuana.[103] Therefore, the overlapping neural regions in both the limbic and paralimbic regions and the regions associated with cognitive control support the inter-relatedness of delay discounting and alcohol demand.

These neuroeconomic findings provide key insights into excessive delay discounting observed in substance dependence and have guided the development of a conceptual model of addiction[104] referred to as the competing neurobehavioral decision systems view. This conceptual model posits that the impulsive decision system and the executive decision system are in regulatory balance for those who can manage appetitive behaviors such as substance use. For those with addiction, the impulsive decision systems exhibit relatively greater control (hyperactive), and the executive decision system exhibits relatively less control (hypoactive).[105,106] Importantly, delay discounting provides a behavioral measure of the relative control of these two decision systems. Although many other dual regulation systems have been proposed, few are specifically focused on addiction.[104,107] Moreover, the conceptual model of the competing systems has been supported by results of interventions directed at either increasing the hypoactive executive decision system or decreasing the hyperactive impulsive decision system.[108]

Derived from the competing neurobehavioral decision systems view is the concept of reinforcer pathology, which has been recently developed within the field of behavioral economics.[102,105,109] The central feature of reinforcer pathology is the interaction between delay discounting, demand for substances, and valuation of substances. Specifically, delay discounting functionally measures the temporal window over which reinforcers are integrated. Substances and some food items deliver a brief, intense reinforcer with immediate and reliable effects, whereas prosocial reinforcers such as ones' work or relationship with others function at lower intensity, are more variable in availability, and have greater value when considered over longer time periods.[110] If the temporal window associated with delay discounting is constricted (high discount rates), then prosocial reinforcers will be viewed over a short time frame and valued less than if viewed over a longer period. Thus, a constricted temporal window increases the relative reinforcing value of substances as the competing prosocial reinforcers are valued less. This process is considered self-perpetuating because use of addictive commodities adversely affects access to alternative commodities. Frequent drug use often results in diminished sensitivity to intrinsically reinforcing stimuli such as food and exercise,[111,112] and this reinforcer pathology process may permit a novel scientific understanding of how prosocial anhedonia is consistent with an allostatic view of addiction.[113] Note that this scientific concept does not function as a diagnostic term, but rather as a research guide.

This model is supported by cross-sectional findings that persons with higher delay discounting rates and alcohol valuation have greater alcohol problems.[114] The best empirical evidence for the reinforcer pathology concept comes from interventions that alter delay discounting rates, such as episodic future thinking (EFT). EFT, derived from the science of prospection, refers to simulating possible prospective events in one's personal future.[110] Prospection entails prefrontal brain structures and contributes to the science of cognitive motivation.[115] Prospection deficits have been observed in those with alcohol use disorders.[116] Presumably, this contributes to reinforcer pathology because it limits the window of time over which they integrate reinforcers. EFT has been demonstrated to involve two different brain regions. First, it tends to increase the utilization of some of the brain areas often associated with delay discounting (e.g., lateral PFCs and anterior cingulate). Second, EFT increases the activity and involvement of other areas not usually reported in imaging studies of delay discounting (e.g., amygdala and hippocampus).[117] Previous research demonstrated that EFT enhances consideration of the future (decrease delay discounting) and/or decreases substance valuation or intake in a variety of disorders including, but not limited to, alcohol use disorders,[118] cigarette smokers,[119] and overweight and obese individuals.[120,121] Therefore, EFT robustly reduces delay discounting and a variety of reinforcer valuation measures in several populations, consistent with the concept of reinforcer pathology.

Neuroimaging and neuromodulation research in exercise and eating

The final section of this review describes experimental health neuroscience research pertaining to two behaviors that together form the core target of many chronic disease prevention efforts: exercise and eating. In the case of exercise, brain-as-outcome methods have been used as a means for quantifying the relationship between variability in fitness levels in the general population and brain health outcomes, as well as the impact of training protocols on the same outcomes. Inherently, this research is also relevant to the prevention of cognitive decline and neurodegenerative disorders, from a brain-as-mediator perspective. In the case of eating, the brain-as-causal-agent perspective is explored, with a focus on experimental research involving noninvasive brain stimulation methods (NIBSs; also known as neuromodulation). Both eating and exercise are of central importance in relation to imbalanced energy dynamics within the body (too much ingested and not enough expended) and the resultant health hazards associated with excess body weight and frank obesity.[122,123] There is an increasing consensus that all levels of obesity confer health risk and diminishing evidence of a protective effect.[124]

The relative contributions of genetics and environment to body mass have been long debated. Increasing rates of obesity in populations that are exposed to highly available and frequently cued calorie-dense foods have focused societal and scientific attention on the possibility of environmental causation of excess body weight.[122,125,126] With respect to genetics, in a recent meta-analysis of genome-wide association studies, collectively involving more than 340,000 individuals, scientists identified 97 single-nucleotide polymorphism loci that reliably predict body mass.[127] Although these loci collectively account for only about 2.7% of the variability in body mass, approximately 21% of body mass variation within the general population could be accounted for by genetic variation from these combined with as-yet-unidentified genetic loci.[127] The analysis of the 97 loci already identified largely implicated the central nervous system in obesity development more so than any other bodily system (e.g., cardiovascular, digestive, endocrine, immune, or respiratory systems[127]) suggesting a fundamental functional interconnection among genes, the central nervous system, and body mass. The mechanism for genetic influence on BMI is not fully understood, but two primary candidates are sweet taste sensitivity and cognitive control resources, both of which appear to have some genetic basis.[128,129]

When seeking to understand one half of the energy balance equation (i.e., energy intake through eating), some have proposed hybrid theories linking brain processes and the social environment, such that evolved characteristics—some of which may be genetically encoded—interact with the modern environment to produce excess body weight.[7,130] One variant of this perspective builds partly on the proposition that humans have a reliable preference for calorie-dense foods due to longstanding evolutionary pressures.[131,132] The mechanism by which such preferences may operate on eating behavior likely involves valuation processes as well as state-dependent visual attention capture.[74,133,134] This perspective is outlined with a focus on studies involving the use of NIBS techniques in the section that follows.

The social neurobiology of food consumption

Mammalian taste buds are tuned for detecting two food object attributes that may have special evolutionary significance: toxins (e.g., bitter taste) and calorie density (e.g., sweet tastes).[135] For approximately 18 million years (from 20 million years ago to about 2 million years ago), human primate ancestors evolved in tropical jungle environments characterized by high plant diversity and the potential for toxin ingestion, thereby driving natural

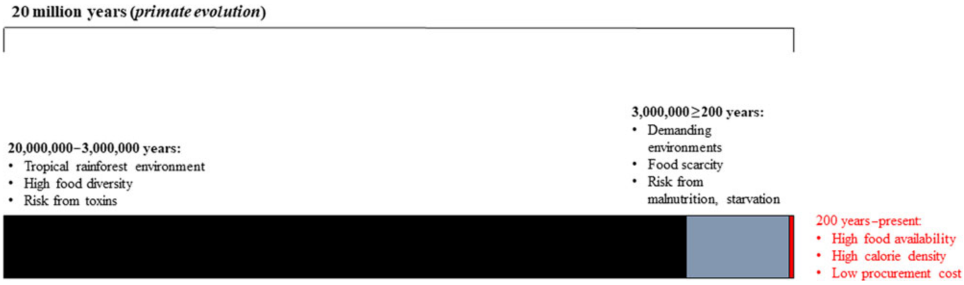

Figure 3. Evolutionary timescale for primates (hominids) contrasted with energy demand and food access characteristics.

selection for toxin detection in foods that remains strong to this day, in the form of evolved aversion to bitter tastes (Fig. 3). An evolutionary bias for sensing calorie density may be of more intermediate origin, coinciding with the emergence of *Homo sapiens* from the tropical rainforest (~ 2 million years ago) into radically different environments where food availability would have been unpredictable and irregularly distributed (temporally and geographically). In such a context, calories invested in the energetically costly process of hunting, gathering, or food cultivation would be more likely to be returned via food ingested when calorie-dense food options are preferentially detected, pursued, and consumed. Likewise, wasted time and energy directed toward nonnutritive food would be avoided with a default preference to seek out and pursue calorie-dense food options.[7,132] The disjunction between palatability and nutritive value is pervasive in the modern food environment characterized by synthetic products, additives, and high-yield agriculture, but the phenomenon of "empty calories" is comparatively rare in naturally occurring food sources that would have been the only options during the vast majority of our evolutionary history as *Homo sapiens*. Ubiquitous food product marketing may further amplify calorie-seeking tendencies by generating frequent instances of needing to modulate the impulse to consume to excess.[136]

Although self-control as a psychological construct has historically been a subject of inquiry,[137–139] the identification of specific brain systems involved has been ongoing for only a few decades. The predominant foci in neuroimaging research are reward signaling mechanisms[140] and reward-modulating control systems.[13,14] Investigations involving fMRI consistently link food-cue related activations of the limbic system with heightened weight and or body composition, as discussed earlier. Reward system hypoactivation,[141–143] hyperactivation,[28,144–147] and dynamic models reflecting both hypo- and hyperactivation[148] have all received some level of empirical support, but also point to the complexity of reward processing involving food.[140]

Recent studies employing NIBS methods have informed our understanding of the role that the dlPFC (Fig. 1) plays in modulating eating behavior that occurs outside of homeostatic need. Two primary variants of NIBS techniques are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS).[149,150] rTMS employs a coil placed over the skull to direct a series of magnetic pulses in predefined patterns to induce changes in excitability of targeted neuron populations within brain regions. The specific pattern of magnetic pulses determines whether the net effect is excitatory (akin to long-term potentiation) or inhibitory (akin to long-term depression), and other parameters determine the duration (see Ref. 151 for a methodological overview). For instance, rTMS variants such as intermittent theta burst stimulation and continuous theta burst stimulation (cTBS) generate net excitatory and inhibitory effects, respectively;[152,153] when targeting the PFC, theta burst stimulation protocols appear to have reliable effects on cognitive task performance in theorized directions.[154] With respect to phenomena relevant to energy intake, meta-analytic reviews involving several appetitive substances—including but not limited to food—have consistently linked excitatory stimulation targeting the dlPFC with reductions in cravings.[155,156]

rTMS and tDCS technologies can assist in testing the causal role of the dlPFC in relation to the modulation of food cravings and consumption, particularly when combined with neuroimaging paradigms. For instance, a recent study randomized female participants for the active or sham cTBS targeting of the left dlPFC followed by an opportunity to consume calorie-dense and less appealing control foods.[157] The findings revealed that cTBS attenuated neural activity—assessed via EEG—commonly linked to executive control, and also caused increased food consumption when a consumption opportunity was subsequently presented. These findings were consistent with those of a recent meta-analysis[156,158] examining all published and unpublished studies using NIBS methods to modulate dlPFC activity (both excitatory and inhibitory); this aggregate statistical summary revealed that neuromodulation produces changes in cravings in the theorized directions, with inhibitory stimulation reliably producing amplification[159,160] and excitatory stimulation resulting in attenuation[161–164]of the craving response to food. Actual food consumption also mirrors the above effects, with experimental studies largely showing moderate-sized effects on appetitive food consumption following dlPFC modulation.[156] Several multisession intervention trials have likewise shown promising effects of repeated administration of dlPFC modulation on weight and eating outcomes[165–167] although the feasibility of such treatments for population-level problems such as overweight and obesity is not fully clear (along these lines, exercise may be a superior population-level strategy, not only because of its effects on metabolism, but also its effect on brain health[168]).

There were two facets of the Lowe and colleagues' study[157] findings that were particularly revealing, however. First, the attenuation of the dlPFC via cTBS selectively increased consumption of calorie-dense food options, while consumption of less appealing options was left largely unaffected. Second, a mediational analysis found that while cTBS also affected cravings, attentional bias (toward calorie-dense foods), and evaluative processes, none of these mediated the effects of cTBS on actual consumptive behavior. That is, attenuation of the dlPFC resulted in stronger cravings, more attention allocated to calorie-dense foods, and more positive valuation of such foods; however, these effects occurred largely in parallel to cTBS effects on eating behavior itself and did not explain the effects on eating. The only reliable mediating pathway linking cTBS effects to eating behavior was via inhibitory control itself. The latter is potentially interesting given that inhibitory control can be accomplished via direct and indirect routes. The former implies inhibition of subcortical reward systems, whereas the latter alludes to competition for working memory resources (i.e., between alternative goals of indulgent eating versus restraint, for instance).

Subsequent findings provide some possible support for the indirect route.[169] In a set of two experimental studies again involving cTBS and eating, left dlPFC attenuation resulted in clear facilitating effects on indulgent thought processes typically subserved by working memory. In this set of studies, indulgent thoughts about food dominated conscious cognition following active stimulation compared to sham, an effect that was evident when participants sampled appetitive snack foods initially to provide a high level of visceral engagement (study 1; Fig. 4), but not in the absence of such visceral engagement. These and other mechanisms remain to be further explored, but NIBS methods will undoubtedly play an important role in examining the causal mechanism from cueing to overconsumption of calorie-dense foods.

Physical activity and brain health

Preventing cognitive decline and the development of neurodegenerative diseases are important public health objectives for older adult populations. Likewise, fostering optimal brain development and maturation may improve physical, social, and mental health outcomes in childhood and adolescence. A necessary prerequisite for achieving these objectives is identifying controllable factors that facilitate brain health.

A substantial body of evidence suggests that physical activity may have brain health benefits throughout the lifespan. For example, cross-sectional and prospective observational studies have found that engaging in greater amounts of physical activity is associated with better cognitive function in older adults[170] and a reduced risk of experiencing cognitive losses or impairment.[171,172] In children, higher levels of activity are routinely associated with elevated executive function as well as better academic performance.[173] These cross-sectional and observational studies are enlightening and informative, but they lack the ability to provide information about the causal nature of the

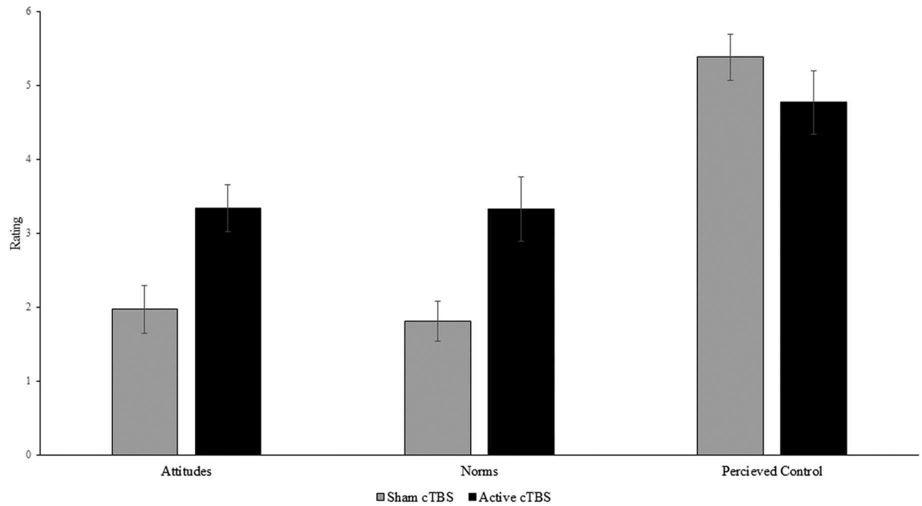

Figure 4. Social cognition pertaining to calorie-dense foods following initial sampling of such foods; higher scores indicate more positive attitudes, more permissive perceived norms, and lower perceived control ratings in relation to calorie-dense foods. Active, active cTBS stimulation targeting the left dlPFC; Sham, sham stimulation. Adapted from Hall and colleagues.[169]

association between physical activity and cognitive function. The most convincing evidence for such an association is demonstrated by randomized clinical trials (RCTs). In a typical RCT, generally inactive adults are randomly assigned to either a treatment group that receives physical activity for several weeks or months or to a control group that is often an attention control group receiving light intensity activity for the same amount of time as the treatment group. In these studies, the physical activity training group often shows improvements in measures of executive function (i.e., working memory, switching, and attentional control), while the control group shows negligible changes.[174] In several meta-analyses, exercise RCTs find that engaging in moderate-to-vigorous physical activity is associated with improvements in several cognitive domains, but mostly in executive function in older adults and impaired populations.[175–177] This research strongly suggests that physical activity (1) is capable of improving cognitive performance in older adults who are at an age where cognitive decline is ubiquitous, (2) is capable of improving executive function in children when the development of regulatory and inhibitory control processes is important for self-control and reducing sensation-seeking behaviors, and (3) that the effects do not appear to be uniform across all cognitive domains—those tasks that measure executive functions are more consistently affected than other cognitive domains.

The research described above suggested that brain regions that support executive functions might be more affected by physical activity than other brain areas. In a series of studies examining the effects of physical activity and fitness on brain morphology using magnetic resonance imaging techniques, Colcombe and colleagues demonstrated that higher fitness levels offset an age-related reduction in gray matter volume in the prefrontal and parietal cortices.[178] In another study, 6 months of exercise in an RCT resulted in an increase in gray matter volume in the lateral PFC and the anterior cingulate cortex,[179] areas known to support executive functions. These studies on brain morphology have been replicated by other, more recent studies.[180] However, in addition to the promoting effects of physical activity on the PFC and anterior cingulate cortex, the hippocampus has also proven to be a brain region that is highly sensitive to the effects of physical activity. For example, in one 12-month exercise RCT, moderate intensity exercise increased the size of the hippocampus in older adults, a region that supports episodic memory function and that typically deteriorates in late adulthood.[181] In sum, there is a significant body of research demonstrating that physical activity influences the morphology of structures supporting both executive function and episodic memory in late adulthood. Similar effects of physical activity on gray matter and white matter morphology have been demonstrated across the lifespan.[182–184]

Gray matter morphology is only one metric of brain health. Other measures of brain health have also shown effects of physical activity or fitness. For example, fMRI methods have found that higher fitness levels and exercise RCTs are associated with significant changes in brain activation during tasks that support executive function.[173,185–187] Furthermore, exercise RCTs have found that resting state networks are modified by engaging in physical activity,[188,189] especially in areas including the hippocampus, PFC, and anterior cingulate cortex. Finally, measures of white matter microstructure as measured through diffusion-weighted imaging have also shown promising effects. In one 12-month RCT, greater changes in cardiorespiratory fitness levels were associated with greater increases in fractional anisotropy, a general measure of white matter integrity.[190] Along these lines, cross-sectional data indicate that higher cardiorespiratory fitness levels are associated with greater white matter integrity, primarily in areas that support communication between the PFC, hippocampus, and posterior brain regions.[191]

In sum, there is promising evidence for the benefits of physical activity on brain health and its cognitive sequelae. We still have much to learn about the mediators of these effects[192–194] and moderators of the effects.[192,195] However, there is clear recognition that the effects of physical activity extend beyond cognitive function[196,197] and how physical activity-induced changes to the brain mediate changes in these and other behavioral outcomes is an important avenue for future research.

Beyond the brain-as-mediator and brain-as-outcome approaches, there is emerging evidence that the brain can also be employed as a predictor of physical activity behavior occurring in both structured (exercise classes) and unstructured (everyday life) contexts. Given that consistency in physical activity requires advance planning, avoidance of distractions, and negotiation of competing sedentary behaviors, there is a conceptual connection between brain processes engaged in multiple cognitive domains, ranging from inhibitory control, attention, and memory, to aspects of affect, motivation, and personality traits. Two recent fMRI studies have sought to use the brain-as-predictor approach to identify the neural predictors of adherence in the context of structured physical activity trials where adherence can be precisely measured. The first investigation—examining data from two exercise trials involving older adult women—found that larger lateral prefrontal volume predicted better adherence over the 1-year interval of the two trials; whole brain analyses revealed other structural predictors including the insula and temporal cortices.[198] A second investigation by Gujral and colleagues examined adherence in older adults using both morphologic and white matter tract microstructure; findings from this study suggested extensive whole brain involvement in adherence, including (but not limited to) the lateral PFC, hippocampus, and amygdala. Superior white matter integrity of the superior longitudinal fasciculus and other tracts also predicted better adherence.[199] All of the above supports the possibility of mutual reinforcement of activity and brain health over the lifespan,[200] a dynamic relationship that is increasingly incorporated into theoretical models of physical activity behavior.[201]

Conclusions and future directions in disease prevention

Advances in neuroimaging, neuromodulation, and population health have revolutionized the way in which we view the brain and its relationship to chronic disease. In addition to being measurable—in more sophisticated ways than ever before—as an outcome of disease processes, the brain is increasingly viewed as a mediator, a moderator, a predictor, and even a causal agent, in relation to chronic disease incidence. Cross-cutting themes pertaining to brain processes in value-based decision making, persuasive communications, delay discounting, and self-control have relevance for primary preventative activities in relation to every major form of chronic disease, from cancer to cardiovascular disease to type 2 diabetes, and the behaviors that give rise to them (i.e., inactivity, substance use, and excess caloric intake). Causal effects of brain processes on the suspension of default preferences for calorie-dense foods and experimental evidence about the brain health benefits of exercise would not have been quantifiable before the advent of neuromodulation methods such as rTMS and neuroimaging methods such as fMRI. These two lines of research serve to advance significantly our understanding of excess body weight, how to manage it, and how to preserve brain health in later life. Rather than supplanting prior conceptual work on behavior and communication, neuroscience methods allow us to test older predictions in new ways, and to augment earlier lines of inquiry with novel (and testable) predictions. Disease prevention initiatives in the future may be increasingly informed by the field of neuroscience, and, accordingly, the integration of neuroscience concepts, methods, and empirical findings may be increasingly useful for the practice of disease prevention on the level of whole populations.

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Competing interests

The authors declare no competing interests.

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