Peter A. Hall *Editor*

Social Neuroscience and Public Health

Foundations for the Science of Chronic Disease Prevention

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Preface

A Brief Orientation to the Volume

The intellectual heritage of public health includes epidemiology, health services, community health, urban planning, and biostatistics. It most clearly does not include neuroscience. This is largely because of the vastly divergent epistemic stances of public health and neuroscience, rather than lack of mutual relevance. Neuroscience is, by definition, highly scientific in perspective and makes great use of the experimental method. Public health is, by definition, highly applied and makes great use of non-experimental or at most quasi-experimental methods. Though these characterizations—like any generalizations—are not without exception, they are largely accurate, at least as these fields have existed up until recently. However, despite differences in conceptualization and execution, the potential for synergy between public health and neuroscience is making it impossible to keep them from each other any longer. My hope is that the production of this volume—the first of its kind—spanning public health and social neuroscience, will illustrate some of the most important synergies, and thereby encourage co-evolution of both fields into the future.

What is in a name? *Public health* is somewhat difficult to define, because it as much refers to an approach to understanding health and illness, as much as it is an area of accumulated knowledge about the determinants of these same things. However, public health minimally involves the examination of the determinants of health from the individual, social, and societal levels, as well as a focus on the prevention of illnesses (or preservation of health) through action at all of these same levels. *Neuroscience*, on the other hand, is the study of the nervous system, its components and its functions. Although much of neuroscience can be reduced to biology, the study of brain and behavior is characteristic of two of the largest and most dynamic subfields: cognitive neuroscience and social neuroscience. These two are the subject of this particular book. Although the title would suggest that social neuroscience is more focal than cognitive neuroscience, in fact the two are not at all separable, and might best be termed "social cognitive neuroscience". Descriptively, one might think of this branch of neuroscience as mostly concerned with the brain (rather than the entire nervous system, including peripheral nerves

for example), and some of the interactions among brain and behavior that have social relevance.

This volume includes a review of several areas of research that exemplify important points of interface between neuroscience and public health. In the next section, I will provide a brief introduction to each.

Theoretical Perspectives

Theory has always played an important role in public health. From the publication of Rose's now classic volume, *the Strategy of Preventive Medicine* (Rose 1994), those seeking to influence disease incidence on the level of the whole population have been necessarily oriented toward statistical representations of population health trends, and abstract concepts/constructions regarding distributions of disease. Explanations of person-environment transactions that have relevance for health have also focussed squarely on theoretical models. As such, theory is woven into the very fabric of public health. In this first section of the book ("Theoretical Perspectives"), we present three perspectives on health behavior: first, from the perspective of Picoeconomics (Chap. 1; Ainslie 2013); second, the MCII process for behavior change (Chap. 2; Gallo et al. 2013); and lastly, Temporal Self-regulation Theory (Chap. 3; Hall and Fong 2013). These models suggest an approach to understanding individual behaviors within the population with reference to interactions among brain-based cognitive processes and the ecological context. Ainslie (2013) describes a process of negotiation among competing interests within the mind, and how the brain valuates temporal proximity to assist in this process. Gallo et al. (2013) discuss the process of furnishing implementation intentions, coupled with contrasting present and future states to generate effective pursuit of health-related goals. Finally, Geoffrey Fong and I outline a new model for individual health behavior, positing a role for brain-based self-regulatory resources in explaining health behavior trajectories (Hall and Fong 2013).

Health Communication

Health communication is the second section of the book, reflecting the second major area of public health's considerable reach. In this section, the contributions discuss research pertaining to the effects of media on brain processes, and the predictive power of such invoked effects. Cascio et al. (2013) (Chap. 4) discuss the multiple roles that brain processes have in health communication, and describe fascinating findings from "neural focus groups" showing that in some cases brain responses to advertisements predict uptake of health resources substantially better than traditional focus groups. Next, Ho and Chua (2013) (Chap. 5) describe the role of self-related processing, and activation of associated brain regions, as being

central to understanding the potential influence of health communications on target audiences.

Health Behaviors

In Part III, we present several submissions documenting the fundamental interconnectedness of brain resources and health behavior performance. Panos et al. (2013) (Chap. 6) describe more than a decade of research linking impaired executive function with poor adherence among those living with HIV. Mullan (2013) (Chap. 7) describes the bidirectional relationship between alcohol usage and executive control resources, and provides important directions for new research in this area. Hagger and Chatzisarantis (2013) (Chap. 8) describe contemporary research on depletable self-regulatory resources, and hypothesizes some biological basis for these. Finally, Galeema et al. (2013) (Chap. 9) describe an incentive-based approach to behavior modification, that might have some connections to the neural mechanisms of reward.

Social Connections, Socioeconomic Status and Stress

How people connect to other, and the nature of their social world has always been a mainstay of public health. Socioeconomic status, relationship quality, and fundamental sense of belongingness have been recognized as important determinants of health. Likewise, stress associated with social positions and social connections have been of interest as long as such associations have been documented. Important new developments have emerged in the ways in which such interactions and repercussions have implications for physiology and brain development. Way (2013) (Chap. 10) discusses the implications of social connection for stress responsivity via neurochemistry, and the brains role in modulating this relationship. Ohira (2013) (Chap. 11) discusses the brain regions activated by stress appraisals, and the potential for brain modulation of immune response parameters. Walach and Loef (2013) (Chap. 12) reflect on the link between social position, nutrition, and brain development. Finally, Galarce and Kawachi (2013) (Chap. 13) describe the role for early adversity in the development of cognitive control resources, and some of the complexities involved in interpretation of existing research in this area.

Exercise Neuroscience

The last content area of the volume describes some of the most important research to come from the physical activity/exercise literature in decades; it falls under the umbrella term, “exercise neuroscience”. McAuley et al. (2013) (Chap. 14)

describe prior research in adult and child populations showing that exercise (and specifically aerobic exercise) benefits the areas of the brain that aid in cognitive control and memory (the prefrontal cortex, and the hippocampus), and describe the implications of these for functional independence in older adults, and academic achievement in children. Next, Matsui and Soya (2013) (Chap. 15) describe fascinating research suggesting that brain glycogen supercompensation may be responsible for some of the beneficial effects of exercise on cortical function. Finally, Liu-Ambrose and Nagamatsu (2013) (Chap. 16) discuss some of the potential benefits of resistance (i.e., strength) training for brain health in older adult populations.

Methods Primer

Lastly, we have three chapters describing methods commonly used in the neurosciences that will serve as a primer for those unfamiliar with some of the techniques used in this volume. Elias (2013) (Chap. 17) describes EEG, fMRI, and other functional neuroimaging techniques used in the neuroscience literature in a way that should be highly accessible to the non-expert readership. Dubin and Hall (2013) (Chap. 18) describe an epidemiological technique—survival analysis—using an application from the new field of cognitive epidemiology. Finally, Lowe and Hall (2013) (Chap. 19) introduce the technique of Transcranial Magnetic Stimulation (TMS) and apply it to examining causal effects of cortical stimulation on food craving and dietary choice behavior.

For ease of review, each chapter begins with several highlights listed in bullet point form, and concludes with a statement about potential policy/applied implications. The writing is intended to be accessible to both public health and neuroscience audiences, but also those in associated fields, including general medicine, epidemiology, sociology, psychology, and economics.

My hope is that this volume serves as a starting point for dialogue between public health and the neurosciences. A great deal of mutual benefit may come from such communication, and the growth of both fields during the next century very much depends on it.

Reference

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Peter A. Hall, PhD, CPsych, is an associate professor of applied health sciences at the University of Waterloo (UW), where he is jointly appointed to the School of Public Health and Health Systems and to the Department of Kinesiology (Neuroscience research group). Dr. Hall is a past recipient of the Canadian Institutes for Health Research (CIHR) New Investigator Award, and an Early Career Award from the Canadian Psychological Association (Health Psychology section). He is founding director of the UW Social Neuroscience and Health Laboratory. His research examines the joint contributions of social-cognitive and neurocognitive factors to the production of health behavior trajectories in everyday life. Dr. Hall serves on the editorial boards of Health Psychology and Journal of Behavioral Medicine, and he is associate editor for the Encyclopedia of Behavioral Medicine, as well as the forthcoming Springer volume, Behavioral and Social Science in Medicine. He is a licensed clinical psychologist and has more than a decade of experience providing clinical services to chronic illness populations in multidisciplinary healthcare settings.

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Part I
Theoretical Perspectives

Chapter 1
Picoeconomics in Neural and Evolutionary Contexts

George Ainslie

Picoeconomics studies the implications for motivational science of nonexponential delay discounting. Many of these can only be mentioned in this chapter, but all except the most recent publications under the author's control can be downloaded from www.picoeconomics.org.

Reward is the selective principle of choice, a process that has presumably been selected in turn by evolution to be a proxy for fitness. However, addictions and other maladaptive behaviors are often strongly rewarded, raising questions about both the unity of the person and the efficiency of natural selection. This divergence of rewardingness from fitness can be accounted for by the apparently inborn form in which we discount prospective rewards as a function of their delay. Nevertheless, the survival of this form in evolution makes sense. Here I will review a rationale developed elsewhere for how this form generates both motivational conflict and somewhat imperfect means of resolving it (Ainslie 1992, 2001, 2005), and discuss relevant research, particularly the neuroimaging studies that have begun to go beyond the simple anatomy of motivation. I will also suggest evolutionary and historical frameworks for the conflict between impulse and control.

Motivational Conflict is Temporal, Not Spatial

An individual's mind is sometimes likened to a society, with some parts acting as dictators or democratic leaders of others (Kuhl 1994; Ryan et al. 1997)—just as Freud (1920, p. 20) speculated that the id could be experiencing pleasure while the ego had unpleasure. The same kind of model has been applied to the brain, with functional centers or even individual neurons competing as if they were rewarded

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independently. Certain brain sites have been reported to be differentially active while particular motives are dominant, such as the amygdala in fear, the insula in disgust, and the orbital frontal cortex in anger (Calder 2003; Ekman 1999). Disconnection of these sites by trauma or experimental manipulation can produce behavioral anomalies such as failure to weigh losses against gains (Bechara 2004), working for rewards the subject does not seem to like (Berridge 2003, 2009), or even obstructing with one hand what she is trying to do with her other hand (Sperry 1984). However, in intact nervous systems motivational influences seem to be well-coordinated, leading to a single evaluation at any given moment. Although different modalities and even time ranges of reward can induce activity in distinct centers, neurophysiological evidence increasingly favors an efficient marketplace that generates unitary preferences at a given time (Carter et al. 2010; Glimcher 2009; Monterosso and Luo 2010; Platt and Padoa-Schioppa 2009). The currency of such a marketplace, reward, must express the value of both near and distant alternatives in the current moment, in weights that are probably experienced as something like emotion (Ainslie 2006; Rick and Loewenstein 2008). To find conflict that goes beyond the simple weighing of these values, we need to look not for divided motivational centers, but for how a person can expect her preference to change over time—what has been called diachronic as opposed to synchronic conflict (Ross 2010).

The analysis of consistency over time and its failure is surprisingly new—newer than that of the functional division of the brain. Olds had already published work on a reward center (e.g., Olds and Milner 1954), and Penfield his map of sensory and motor centers (e.g., Penfield and Jasper 1954) when economist Strotz (1956) broke with classical economics to point out that a person's preferred rate for consuming a good is likely to change over time, even if she has learned nothing new about her options. Even then the article was largely ignored for two decades. It was a finding in behavioral psychology, Herrnstein's (1961) matching law that eventually provided a tool for analyzing preference change as a function of delay. The matching law states that choice on concurrent variable interval schedules of reward is proportional to the immediacy of the rewards as well as to their amount and rate of delivery (Chung and Herrnstein 1967). When this proportionality was applied to single discrete choices it predicted that the discounting of delayed rewards would obey a hyperbolic function (Ainslie 1975), rather than the exponential function that had been explicit in economics (Samuelson 1937) and implicit in the other behavioral sciences' assumption that preferences tend to stay consistent in the absence of new information. Many observations in nonhuman animals (Ainslie and Herrnstein 1981; Mazur 1997) and people (Green et al. 1994; Kirby and Marakovic 1995) confirmed this prediction, as well as the related predictions that preference between a smaller, sooner (SS) and larger, later (LL) reward would often shift from LL to SS as delay becomes shorter, and that, with appropriate tools, even pigeons and rats can learn to choose a commitment that prevents them from subsequently acting on the new preference (Ainslie 1974; Deluty et al. 1983). Activity in human cortical reward centers has recently been found to track delay in parallel with the hyperbolic

discount curves that describe the subjects' actual choice behaviors, but the data are still too noisy for a specific hyperbolic function of brain activity itself to be differentiated from an exponential function (Kable and Glimcher 2007).

Economists exploring dynamic inconsistency of choice soon picked up the model of hyperbolic discounting, but proposed a modified, *hyperboloid* shape that grafted a steep rise in value as an SS reward becomes closer on top of a standard exponential curve for all other delays (Laibson 1997). This modification was prompted by the difficulty of using hyperbolic curves in economic models rather than by data (Angeletos et al. 2001, p. 50); but hyperboloid curves have gained intuitive support from the phenomenon in which some rewards are augmented by emotional arousal or appetite, a property sometimes called viscerality (Loewenstein 1996), which suggests a mechanism for the steep rise in a reward's value when it is close. However, many examples of temporary preferences for SS rewards do not involve arousal, such as simple procrastination (Ainslie 2010), short-sighted job seeking (Paserman 2008), and failure to save for retirement. Also, a hyperbolic shape has been observed where the closer alternative is months or decades away (Cropper et al. 1992; Green et al. 2005). Nevertheless, the hyperboloid variant is widely accepted, especially in economics. Because most of the difference between exponential and hyperbolic curves is observed in the period just before the SS reward is due, hyperboloid curves plotted as the sum of a very steep and a shallower exponential curve can fit experimental data as closely as pure hyperbolic curves (e.g., McClure et al. 2007), although the hyperboloid curve requires two parameters while the hyperbolic curve needs only one. Hyperbolic and hyperboloid shapes each can account for a person's inconsistent preference over time, as well as for an incentive for her to commit herself in advance to wait for an LL alternative. However, a pure hyperbolic shape is arguably necessary to motivate people's progression from the discount function we are born with to rational adult patience.

Our inborn discount curve is steep. In both young children and our closest evolutionary cousins, the great apes, the prospect of outcomes delayed by more than a few hours has no value (Atance and O'Neill 2001; Mulcahy and Call 2006). The great increase in patience seen in adult humans is learned, and learned imperfectly. When encouraged to choose spontaneously people often show annualized discount rates of thousands of percent (Ainslie and Haendel 1983; Kirby 1997). An English company even advertizes loans with a 1,734 % annual interest rate (Underground ad for www.QuickQuid.co.uk, June 2012). Measurement of discount rates gives widely varying values among people, and among different kinds of rewards within individuals (Frederick et al. 2002), a finding that contrasts sharply with the narrow range of rates seen within a nonhuman species (Mazur and Biondi 2009; Ainslie and Monterosso 2003). The explanation probably lies not with individuals' inborn discounting tendencies, which always favor SS rewards, but rather with differences in the ways people have learned to compensate for these tendencies so as to manifest shallower and more consistent discount rates.

Internal Self-Control Requires Intertemporal Bargaining

Hyperbolic discounting of prospective reward divides a person into competing interests, not based on competing reward centers but on changing command of a unitary reward network over time. Interests based on delayed rewards will be weaker than interests based on imminent rewards, but they have the advantage of foresight. If such an interest can motivate precommitment of choice or keep a future self from coming too close to an SS reward, it will get the LL reward on which it is based. If it fails, the SS reward will become stronger and have the last word. *Extrapsychic* precommitments include medicines that change appetite, contracts, illiquid investments (Laibson 1997), and especially social environments. *Intrapsychic* commitment in advance is also possible, but to a limited extent: A dominant interest can restrict attention or inhibit specified responses for a period of time, but can remain vigilant only so long against the weighing of alternatives. Like price controls in an otherwise free market, restricted attention builds up contrary motives. Response inhibition can be seen in experiments where subjects have to resist an urge, for instance saying the color names instead of the print colors in a Stroop task or waiting for a signal in a go/no-go task. The many studies on this kind of task have found it to be associated with activity in the dorsolateral and ventrolateral prefrontal cortices and anterior cingulate gyrus (e.g., Chambers et al. 2009), but it is almost certainly not the process that stabilizes intentions over long periods of time (Monterosso et al. 2010). People can also learn what trains of thought lead to the appetite for an impulse—for instance, the Catholic church's "venial sins" (Holton 2009)—and derail them before they become too attractive; but again this method requires forestalling the impulse in advance.

A need for commitment in advance implies a fragility of internal self-control, sometimes called weakness of will. Willpower does more than commit against temptations. With willpower a person tests herself against temptations while "both alternatives are steadily held in view" (James 1890, p. 534), and feels an emotional loss—guilt—if she fails. A mechanism that does not involve separate motivational faculties has been elusive: What self can be said to control what other self? However, a rationale can be derived from the high tails of hyperbolic discount curves that depict the value of LL alternatives at relatively long delays. The tails of hyperbolic curves are much higher than those of exponential curves—and of hyperboloid curves, which, by definition, are the same as exponential curves when the rewards are not imminent. The difference is especially pronounced where a person interprets the value of a current choice to include the value of a bundle of similar choices that she expects to make in the future. To illustrate the difference in the values of bundled rewards, Fig. 1.1 shows a series of four rewards, discounted exponentially versus hyperbolically, at rates adjusted to make the value of a reward of amount 10 worth 1 at 10 units of delay.

Even added together, the exponentially discounted value of the bundle soon falls to a tiny fraction as delays get longer, just as that of single reward does (e.g., the last reward in the series if the curve were not augmented by the others). By contrast, the hyperbolically discounted value remains relatively high, falling more and more slowly as delays get longer.

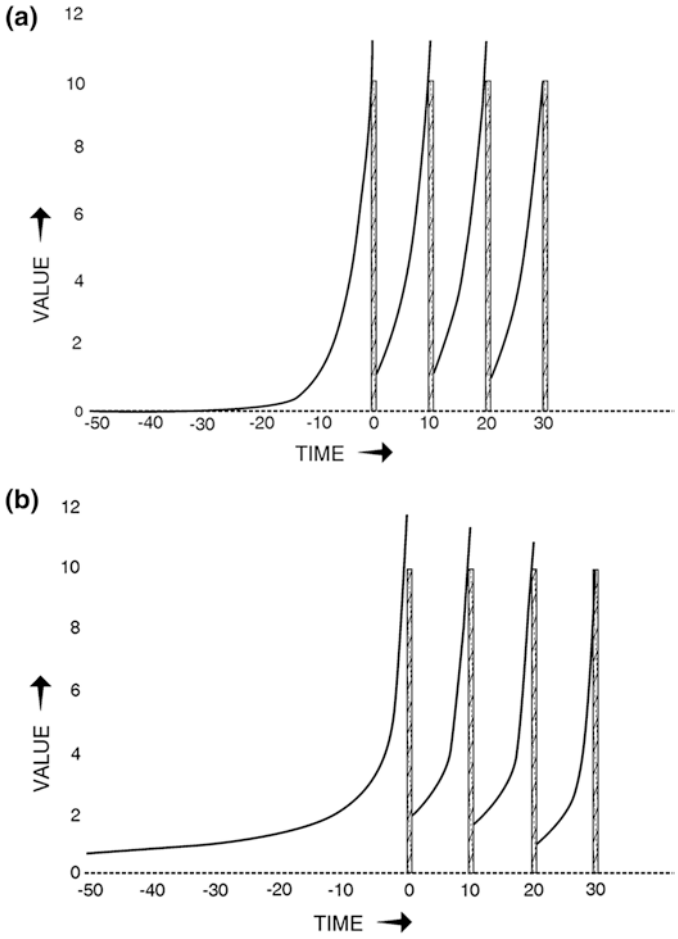

Fig. 1.1 **a** Cumulated exponential discount curves from 4 rewards of 10 units each, separated by 10 time units. The value of the single (*right-most*) curve is set to 1 reward unit at 10 units of delay ($\delta = 0.794$, where Value $=$ Value$_0$ $\times$ δ^{Delay}). At 10 time units before the first reward, the whole bundle is worth only 1.111 ($1.0 + 0.1 + 0.01 + 0.001$). This figure could also describe the δ portion of β–δ curves; the β portion, which by definition is not anticipated, would just make each curve higher at near-zero delays. **b** Cumulated hyperbolic discount curves from 4 rewards of 10 units each, separated by 10 time units. As in Fig. 1.1a, the value of the single (*right-most*) curve is set to be 1 reward unit at 10 units of delay (here k $= 0.9$, where Value $=$ Value$_0$/[1 + (k x Delay)]). Ten time units before the first reward is due, the whole bundle yields a value of 2.15 ($1.0 + 0.526 + 0.357 + 0.270$). As the curve passes 50 units of delay its value is still substantial

I have argued that this bundling effect is what lets people learn to follow the rational norm for exponential discounting, as long as the consequent present deprivation is not too great (Ainslie 1991): In a choice between an SS and LL reward, if she notices that her current choice is a good predictor of how she will make similar choices in the future, her expectation of that whole bundle of future rewards

will come to depend on the meaning she finds in her current choice. That is, to the extent that she interprets her current choice as a test case for a bundle of later rewards, the discounted values of the whole bundle will depend on, and therefore contribute to, her choice (Fig. 1.2; discussed further in Ainslie 2012). This hypothesis has two parts: that choosing a bundle of rewards all at once will increase the value of the LL options; and that a person's interpreting her current choice as a test case will have the effect of creating such a bundle, much as a player's current move in a repeated prisoner's dilemma is based on her expectation of how that move will affect the whole string of her partner's future moves.

There is evidence that the current discounted values of future rewards are additive (Kirby 2006; Mazur 1986), and there are experiments showing that choosing a series of rewards all at once increases preference for the LL alternatives over what it is when subjects choose between the same pairs one at a time, both in people (Kirby and Guastello 2001; Hofmeyr et al. 2010) and in rats (Ainslie and Monterosso 2003). The rat experiment is especially valuable in showing that increased patience for bundled rewards is not an artifact of culture or experimenter suggestion, but presumably based on the raw rewarding effect depicted by the discount curves.

However, the second part of the hypothesis is harder to test. The person's weighing of alternatives is proposed to be *recursive*, so if she chooses against the current alternative she reduces her expectation of subsequently choosing LL rewards in similar situations, which may make choice of the current LL alternative relatively more attractive; but this will be true if and only if she expects choosing the SS alternative to reduce her likelihood of getting later LL rewards, *and* expects choosing the LL alternative to increase this likelihood. In exploring the problem she may think of a rationale whereby the current choice is exceptional, and therefore not a test of future prospects; or she may have such a bad record of giving in to temptation

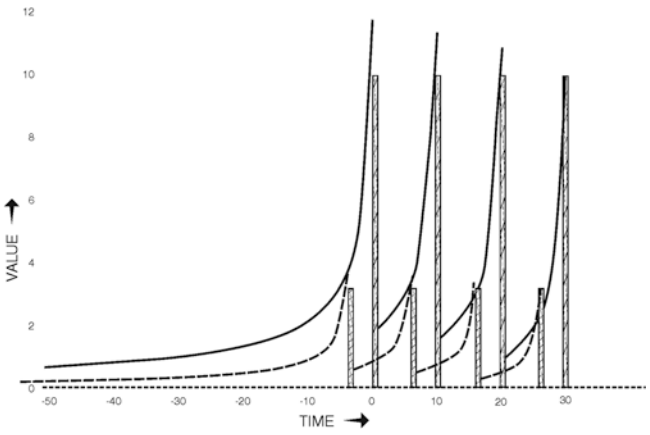

Fig. 1.2 Two alternative series of four rewards each, hyperbolically discounted and cumulated as in Fig. 1.1b. In the single (*right-most*) pair the SS reward is temporarily preferred, but as the values of pairs are cumulated (*moving leftward*) this preference disappears

that one LL choice will not create much hope for future choices. The logic of this *intertemporal bargaining* is much like that of the repeated prisoners' dilemma that defines self-enforcing contracts between individuals (Telser 1980)—the deterrent to defection being not revenge but the loss of expected cooperation in future transactions. Experiments on this internal dialog are hard to design because they represent exceptional cases by their very nature. Nevertheless, there was a finding that suggests recursive self-prediction in each of the two human experiments just cited: Telling a group of subjects who chose between an SS and LL reward every week that their future free choices were apt to be the same as their current choice led to more LL choices than in a control group, though not as much as in a group that had to make all their choices at once in the first week. The phenomenon is better demonstrated by means of a loan from the philosophy of mind, the thought experiment (discussed in Ainslie 2007). Simplest is Monterosso's problem:

> Consider a smoker who is trying to quit, but who craves a cigarette. Suppose that an angel whispers to her that, regardless of whether or not she smokes the desired cigarette, she is destined to smoke a pack a day from tomorrow on. Given this certainty, she would have no incentive to turn down the cigarette—the effort would seem pointless. What if the angel whispers instead that she is destined never to smoke again after today, regardless of her current choice? Here, too, there seems to be little incentive to turn down the cigarette—it would be harmless. Fixing future smoking choices in either direction (or anywhere in between) evidently makes smoking the dominant current choice. Only if future smoking is in doubt does a current abstention seem worth the effort. But the importance of her current choice cannot come from any physical consequences for future choices; hence the conclusion that it matters as a precedent (Monterosso and Ainslie 1999).

It does not matter that the negative effects of some habits, such as smoking, do not come repeatedly and soon after the positive ones, hangover fashion, but only in the far future (as Rick and Loewenstein 2008 have objected). The prospect of future health still forms a stake that is at risk in every choice that the person sees as evidence of her pattern of future choices.

In other contexts feedback from self-testing is a familiar experience. Visceral processes such as anger, panic, nausea, sleep (in insomniacs), and urination (in men with prostatic hypertrophy) are promoted by signs that they are already happening, a phenomenon first described by Darwin, James, and Lange but mistakenly held to be the origin of these processes (Rolls 2005, pp. 26–28). The importance of self-testing in willpower may not be evident when the stakes are low, as in resolving to clean up your office; but it becomes clear when large amounts of incentive hinge on the test, as when a recovering alcoholic decides whether to try drinking just once. The latter case follows the same logic as the decision of a party to a self-enforcing contract to cheat her partner; such a defection by the current self leads to the notorious abstinence violation effect (Marlatt and Gordon 1980; for dieters, see Polivy and Herman 1985). Furthermore, where an appetite-based consumption is restrained by willpower, upticks in the person's appetite may cause reductions in her certainty of control that induce further appetite. Such a vicious circle may produce the sudden cravings that are often implicated in relapses, which have been imperfectly explained by the conventional theory, classical conditioning (discussed in Ainslie 2010).

Where Neuroimaging Might Detect Intertemporal Bargaining

Response inhibition tasks such as the Stroop are easy to study with fMRI, but the imaging of valuation-based self-control is harder, and is less than a decade old. The first fMRI study of SS versus LL choice appeared to show that delayed rewards were evaluated only in frontal cortical sites, not the limbic ones that responded to immediate rewards, a finding that might be interpreted as showing separate reward centers (McClure et al. 2004, 2007). However, other SS/LL studies have shown that all reward-sensitive sites in humans discount delay of reward equally (Kable and Glimcher 2007). The activity in sites associated with human self-control, particularly the dorsolateral prefrontal cortex (PFC) and posterior insula, seem to modulate rather than compete with comprehensive reward valuation centers such as the ventromedial PFC and ventral striatum (Hare et al. 2009; Monterosso and Luo 2010). The imaging of the modulation process is far from providing clear mechanisms, but some suggestive studies have been done.

First of all, the process of weighing alternatives *per se* has been found to alter their value, in a way that favors LL rewards: When subjects anticipate individual SS and LL rewards for which they both previously and subsequently express equal preference, activity in brain reward centers is less when they expect the LL reward than when they expect the SS reward (Luo et al. 2009). Similarly, disruption of left lateral PFC function with transcranial magnetic stimulation decreases choice of LL rewards that had previously been equally preferred to SS alternatives—without changing subjects' reported valuations of the rewards when considered singly (Figner et al. 2010). These findings imply that the process of intertemporal choice itself augments the relative value of LL rewards.

There have begun to be reports of relationships among centers that are specifically associated with LL choice. Combined valuation of food and prospective health in the ventromedial PFC is modulated by activity in the dorsolateral PFC when subjects are exercising self-control (Hare et al. 2009). The oft-noted increase in patience from adolescence to mid-adulthood is accompanied by a greater connectivity of the ventromedial PFC with the dorsolateral PFC and parietal and insular cortices during LL choices (Christakou et al. 2011). When subjects try not to be tempted by cigarettes or food, increases in lateral PFC activity and decreases in reward center activity are correlated with reported decreases in craving, an effect fully modulated by one of the reward areas (ventral striatum—Kober et al. 2010). A further study found that when subjects have to repeatedly reject stimuli previously conditioned to SS rewards in order to get an LL reward, activity in a region of the anterior PFC varies inversely with activity in reward centers, to a greater degree the more successfully a subject resists the lure (Diekhof and Gruber 2010); however, interpretation of this last finding is complicated by its resemblance to go/no-go tasks. Finally, subjects who show more spontaneous alternations of preference between an equally preferred (on average) pair of SS and LL rewards have more activity in another region that is often observed to be active in self-control (left insula/inferior frontal gyrus) when making LL choices, suggesting that inconsistency may elicit more executive function (Luo et al. 2011).

Reports that executive functions in frontal centers modify activity in valuation centers have led to the proposal that there is a third possibility beyond single-valuation and dual-valuation hypotheses, "self-control" (Figner et al. 2010). However, even though lateral PFC activity does not track activity in the ventromedial PFC and other reward centers, it must still depend on the common currency of reward. Some competitive process must still weigh, for instance, whether it is worth the risk to try a single cigarette after a month without smoking, or whether gratifying an angry impulse is worth the harm it would do to your self-image. Executive functions must still compete in the marketplace. Abstract and long-term value must arise somewhere, and be weighed against the value from more tangible sources. This somewhere might even be the same ventromedial PFC that has been seen to weigh tangible rewards, perhaps in a continuous pattern that we cannot presently detect with our episodically based experimental designs. The ventromedial PFC is part of a set of wide, overlapping networks that subtend autobiographical memory, vicarious experience, future projection, and undirected thought (Spreng et al. 2009)—in short, imagination. It has been reported to modify other rewards (Peters and Büchel 2010), but might well be capable of generating reward in its own right, constrained only by the tendency of self-generated reward to habituate (Ainslie in press). Whatever the source, more patient choice has been found to be correlated with activity in the ventromedial PFC when subjects imagine future events (Mitchell et al. 2010). Similarly, presenting subjects with words naming their own expected future events during an intertemporal choice task causes more patient choice, accompanied by activity in the ventromedial PFC and anterior cingulate gyrus (an "episodic imagery network") and increased coupling between this gyrus and the hippocampus (Peters and Büchel 2010). These findings are tantalizing, but the motivational contingencies that induce and constrain the modulating activity of imagination cannot themselves be seen. As long as fMRI can take only snapshots, not movies, direct observation of internal dialog such as recursive self-prediction will not be practical, even if good markers for semantic content (e.g., "this choice is a test case") can be found. Meanwhile, the interaction of a person's alternative prospects might be partially modeled by the fMRI of interacting pairs of subjects—so-called "second person neuroscience" (Schilbach et al. in press)—by analogy to modeling intertemporal prisoner's dilemmas with interpersonal ones (Monterosso et al. 2002).

Evolutionary and More Recent History of Self-Control

Both the steepness and the curvature of our inborn discount curves look maladaptive. They have been implicated in such problems as the named addictions (e.g., Bickel and Marsch 2001) and some less obvious ones such as short-term preferences for overeating, procrastination, passive entertainment, and social disengagement. The question immediately arises of how they could have survived natural selection, but an answer is not hard to find. By the time humans evolved, the basic math of perception was long established. Differences in elementary

psychophysical quantities—brightness, weight, loudness—are experienced proportionately to an index amount, that is, hyperbolically, a phenomenon known as the Weber-Fechner law (Gibbon 1977). For instance, we perceive a change in brightness proportionately to the starting level of the brightness. If delay or some dimension incorporating delay were experienced the same way it would not have caused a problem for nonhuman species, in which long-term interests are protected not by planning but by instinctual incentives to hoard, mate, migrate, and so forth, gratification of which pays off immediately (see Ainslie 1992, pp. 85–88). Reward does not imply adaptiveness; it is only an evolved proxy for adaptiveness, and may be slow to itself adapt to changed contingencies of natural selection. Hyperbolically discounted reward motivates adaptive long-term choices perfectly well when these pay off immediately, in the gratification of instinctive urges. Where rewardingness diverged from adaptiveness was in the radical increase of intelligence that let humans steal pleasure from evolved instincts, and for the first time subjected our welfare to our hyperbolic discounting of future prospects.

Addictions are just conspicuous examples of a widespread phenomenon, capture by short-term rewards, which evolution and even cultural selection have not had time to counteract. Growth of biological immunity to specific addictions is certainly possible. For instance, the prolonged aldehyde dehydrogenase metabolic phase that makes alcohol aversive to many East Asians (Agarwal and Goedde 1989) could, over millennia, spread and become general. Cultural responses can be faster, and arguably have adapted European behavior toward alcohol over the centuries, in contrast to the devastation wrought by its sudden introduction to native American cultures. But the cheap, concentrated substances that cause high addiction rates—distilled grain alcohol, synthetic opiates, purified cocaine, amphetamines—date back no further than the seventeenth century (Austin 1978), and new, fast-paying activities continue to be introduced without our having any idea of their addictive potential (but see King et al. 2011). Modern culture has been slow even to learn about the addiction-prone aspect of human nature, much less to evaluate new hedonic inventions for how they might be exploiting it.

At the genetic level an evolutionary response to impulsiveness might be seen in compensatory processes such as the larger prefrontal cortices, which seem to be crucial for the process of self-control, in *Homo sapiens* than in *Homo heidelbergensis* (DuBreuil 2009). Similarly, delay discounting rate has been reported to be inversely proportional to lateral frontal cortex volume (Bjork et al. 2009). However, even increased self-control may fail to increase fitness in the Darwinian sense because it fosters long-term reward-maximizing solutions that do not prioritize the increase of gene copies—for instance with the choice to use birth control in societies where most offspring survive, and, to a lesser degree, adoption of measures to prolong life into old age. When impulsive behaviors evade control, evolutionary fitness may sometimes increase. To that extent society will have to deal with the consequences of hyperbolic discounting culturally, without net assistance from natural selection.

Historically, the popularity of willpower as a means of impulse control has been associated with the growth of individualism in western society. As late as the

sixteenth century most decision-making was a social process, in which individual interests were overshadowed by those of the family and clan (e.g., Stone 1977). Reliance on social influence for self-restraint is still widespread, and is correlated with personality, gender, and other factors (Gilligan 1977; Smith et al. 1997), but in a cosmopolitan society this extrapsychic device has three notable weaknesses: It leaves the person open to exploitation by others, it does not affect concealable impulses, and it is useless when the person's group as a whole tolerates an impulse. In the sixteenth and seventeenth centuries increasing attention to the individual conscience—the subject of most early diaries (Carroll 1981; Shea 1968)—went along with the theology of predestination, in which a person's whole expectation of salvation was staked on her every choice (Weber 1904/1958). Minus the divine mediation, this process is simply an extreme example of the recursive self-prediction that recruits willpower—making each choice a test case for your expectation of a bundle of later rewards. This nonlinear process makes a person's choices unpredictable in principle from a knowledge of the incentives she starts with, a serious flaw from the viewpoint of economic analysis (discussed in Ainslie 2012), but a solution to the old philosophical conundrum of free will, which demanded that a choice be either uncaused or caused linearly by prior conditions (discussed in Ainslie 2011). Willpower itself, however, is no more an ideal correction to hyperbolic discounting than social control is. It makes lapses hard to recover from, creates an incentive to limit awareness of one's own choice-making, and is apt to make a person compulsive (discussed in Ainslie 2001, pp. 143–160). The development of solutions to the problematic interaction of technical skill with hyperbolic delay discounting may be said to have only started.

Conclusions

With an intact nervous system the simultaneous conflict of motives is not likely to elicit self-control, but only a comparison of values. The incentive for self-control is the prospect that this comparison will come out differently in subsequent choices. Short-term committing devices such as response inhibition have clear fMRI correlates, but correlates of the intertemporal bargaining implied by willpower have barely begun to be explored. Social influence is the other major impulse-controlling factor, but this, too, struggles to keep up with an environment that has moved far beyond the one in which our motivational faculties evolved. Since the way to maximal long-term reward seems to lie in balancing imperfect strategies, the best societal response would seem to be the study and teaching of their counterintuitive motivational bases.

An address to the University of Cape Town, South Africa, September 10, 2012.

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Highlights

- Human motivational conflict is best analyzed in the relationship between present and expected future selves, rather than between separate motivational centers.
- People have inherited a delay discount curve that is probably a pure hyperbola, making us prone to addictions and impulsive behaviors.
- The motivational force of willpower comes from seeing a current choice as a test case that predicts future choices in similar cases (recursive self-prediction).
- Current neuroimaging techniques can reveal the interaction of motivational centers in self-control, but not their semantic content, such as the hypothesized recursive self-prediction.
- Hyperbolic discount curves have survived in evolution because they have a deeply rooted psychophysical form, and are harmless in species whose future planning is instinctive.
- There is no dimension of impulse control that is best maximized, since the major available strategies, social pressure and willpower, both have serious limitations.

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Chapter 2
Neurophysiological Correlates of the Self-Regulation of Goal Pursuit

Inge Schweiger Gallo, Anna-Lisa Cohen, Peter M. Gollwitzer and Gabriele Oettingen

People often struggle with their goals and become very frustrated when they fail to reach them. Sometimes, the underlying problem is that people fail to frame their goals adequately. People may set themselves a prevention goal (i.e., focus is on negative outcomes) where a promotion goal (i.e., focus is on positive outcomes) would have been more suitable (Higgins 1997), or a performance goal (i.e., focus is on one's standing) where setting a learning goal (i.e., focus is on one's progress) would have been the right thing to do (Dweck and Elliott 1983). Most importantly, the chosen goal (e.g., achieving a certain weight loss) should specify an outcome that is perceived as highly desirable (i.e., the estimated attractiveness of the likely short- and long-term consequences of attaining the goal is high) but also feasible (i.e., the perceived probability of success is high; Gollwitzer 1990; Oettingen and Gollwitzer 2001).

Still, selecting and committing to desirable and feasible goals as well as framing these goals appropriately is only a first step to successful goal attainment, as there is always the issue of keeping up one's goal striving in the face of obstacles (Gollwitzer and Oettingen 2012). Here it helps when people anticipate the difficulties or problems they may run into when trying to meet their goals. The obstacles that can challenge successful goal attainment are manifold. They may relate to failing to get started (e.g., procrastination of goal striving), failing to stay on track

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(e.g., falling prey to distractive temptations), failing to call a halt to futile goal striving (e.g., escalation of commitment to a faulty means), and failing to prevent overextension (e.g., getting depleted too quickly). Thus, successful goal attainment not only requires that people choose wisely between possible goals (i.e., select goals that are both desirable and feasible and then frame them appropriately) but also cope effectively with challenges on the way to goal attainment.

The Self-Regulation of Goal Selection

A self-regulation strategy that has been shown to help people to best select and commit to new goals is mental contrasting of future and reality (Oettingen 1997, 2012). This strategy allows people to strongly commit to achieving desired and feasible future outcomes. It implies to first imagine the attainment of a desired future (e.g., do more exercise) and then to reflect on the personal obstacles of present reality that impede attaining the desired future. This juxtaposing of future and reality makes people realize that they have not reached their desired futures yet and therefore need to take action if they want to attain them. As a consequence, people start thinking on whether or not they have a good chance to overcome the personal obstacles that stand in the way. Only when people have high expectations of success will they then strongly commit to the goal to attain the desired, and thus goal realization is promoted; if expectations of success are low, however, people will desist. Thus, mental contrasting helps to discriminate between feasible and unfeasible attractive goals and committing to goals in an expectancy-dependent manner.

Mental contrasting has to be differentiated from another form of thinking about the future known as indulging (Oettingen 2000). Whereas in mental contrasting the present reality is juxtaposed to the desired future, when people engage in indulging they only envision the wished for future; they do not identify obstacles and a necessity of acting to actually achieve the desired future is not experienced. As a consequence, indulging fails to create strong goal commitments; goal commitments stay moderate no matter whether expectations of success are high or low. In contrast, mental contrasting produces selective, expectancy-dependent goal commitment, which in turn produces better goal attainment when expectancies of success are high rather than low (Oettingen 2012). Thus, only mental contrasting produces wise behavior change efforts on the side of the individual (high engagement for change in the face of high expectations of success, and reduced engagement for change when expectations of success are low).

Mental Contrasting Effects and Processes

The differences between mental contrasting and indulging have been analyzed focusing on various indicators of goal commitment. More specifically, research using self-report measures, assessing the behavioral intensity of moving towards

the goal as well as the rate of goal attainment, and taking physiological measures, all have shown that mental contrasting and indulging differ in their underlying cognitive and motivational components and processes. In a series of experiments testing underlying cognitive processes, Oettingen and colleagues showed that goal attainment by mental contrasting is produced by changes in both implicit cognition and energization (overview by Oettingen 2012). Recent research, for example, has revealed that mental contrasting strengthens the associative link between the desired future and reality, as well as between present reality and instrumental behavior; it also leads people to identify negative aspects of reality as obstacles to reaching the desired future. Moreover, mental contrasting effects on goal striving and attainment have also been found to be mediated by motivational processes: mental contrasting increases feelings of energization as well as physiological arousal in high-expectancy participants, whereas it lowers them in low-expectancy participants. Importantly, no such changes are observed in indulging participants.

Neural Correlates of Mental Contrasting

Across studies, mental contrasting and indulging have been found to be two distinct self-regulatory strategies with characteristic effects on goal commitment and attainment. To test whether the postulated differential underlying mechanisms are also reflected at neural basis, Achtziger et al. (2009) focused on the brain activity associated with the strategies of mental contrasting versus indulging. For this purpose, Achtziger et al. (2009) recorded continuous magnetoencephalographic data while participants engaged in either mental contrasting or indulging. Whereas mental contrasting is cognitively very demanding and involves a purpose that one intends to fulfill (i.e., it serves to resolve the issue of whether or not to commit to realizing a certain desired future outcome), indulging has an end in itself. Moreover, in contrast to indulging, mental contrasting requires juxtaposing the present negative reality to the desired future (i.e., working memory) as well as detecting relevant obstacles and answering the question of how one dealt with these obstacles in the past (i.e., episodic memory); all of this should benefit much from vividly imagining the future and relevant present and past events. Thus, a greater activity in brain regions associated with working memory and episodic memory processes, but also with strong intention formation, action preparation, and imagery were expected for mental contrasting as compared to indulging, as the latter only implies free daydreaming.

In the Achtziger et al. study, participants were pre-selected based on how well they did in both mental contrasting and indulging. In this pretest, they were asked to name their two most desired interpersonal future outcomes and their two most desired academic future outcomes. The experimenter then handed out detailed written instructions on how to engage in the two different modes of thought with respect to their desired interpersonal outcomes (i.e., mentally contrasting one and indulging in the other; see Oettingen 2000, Study 1; Oettingen et al. 2001).

Mental contrasting instructions requested participants to list two positive aspects they associated with having the targeted desired interpersonal outcomes and two aspects of present reality that stand in the way of reaching this desired outcome. Thereafter, participants were asked to elaborate these aspects in the following order. First, they were told to imagine events and scenarios related to one of the positive future aspects. Specifically, participants were instructed: "Think about this aspect and depict the respective events or experiences in your thoughts as intensively as possible! Let the mental images pass by in your thoughts and do not hesitate to give your thoughts and images free reign. Take as much time and space as you need to describe the scenario. If you need more space to write, please use the back of the page." Using the same instructions, participants were then asked to imagine events and scenarios related to one of the listed aspects of negative reality. Finally, participants were asked to turn to the other listed positive future aspect, and subsequently to the other listed negative reality aspect.

Indulging instructions were equally detailed. Participants first had to list four positive aspects they associated with having attained the targeted interpersonal outcomes. Participants were then requested to mentally elaborate all four positive future aspects using the instructions cited above. Thus, mental contrasting and indulging instructions differed only in terms of which aspects of the targeted desired interpersonal outcome needed to be elaborated. Each participant had to follow mental contrasting instructions for one, and indulging instructions for the other of the two named most desired interpersonal outcomes; order of instructions was counterbalanced.

For the next day, only those pretested participants were invited to take part in the MEG study who had been judged by independent raters as both effective mental contrasters and effective indulgers with respect to their interpersonal outcomes, and who in addition had indicated high expectations of success with respect to their two named desired academic outcomes. In the MEG study, participants' electromagnetic activity was recorded while they rested for 5 min before being asked to engage for 10 min in mental contrasting of one of the desired academic outcomes listed the day before, and for 10 min of indulging in the other. The order of strategy application was counterbalanced, and a break of 1.5 h duration was placed in between.

In order to assess brain activity, the collected continuous MEG data were analyzed in a rather novel way using the so-called multiple dipole density method (Fehr et al. 2003a, b). Results revealed differential magnetoencephalographic activity for the two strategies of intention formation, thus supporting the assumption that both strategies can be differentiated in terms of their underlying neural correlates. Importantly, the data suggested that mental contrasting is a problem-solving strategy, as higher brain activity was observed in the left prefrontal area as compared to resting and in the right frontal area as compared to resting and indulging. The same pattern of results was observed with regard to both the left and right temporal and the right parietal areas, as more dipoles per second were measured during mental contrasting as compared to resting and indulging. Finally, greater activity was found bilaterally in occipital areas during mental contrasting

compared to resting, as well as the right occipital site for mental contrasting as compared to resting and indulging (see Fig. 2.1). As activity in frontal/prefrontal, temporal, parietal, and occipital areas have been identified as involving working memory, episodic memory, intention formation, and mental imagery, respectively, these results support the assumption that mental contrasting, but not indulging, is a cognitively demanding, problem-solving strategy.

Goal Striving by Implementation Intentions

Holding strong goal commitment is an important determinant of successful goal attainment. However, striving toward one's goals may be hampered by all kinds of challenges on the way to the goal that need to be coped with effectively (Oettingen and Gollwitzer 2010). One powerful strategy that has been shown to help people take control over the implementation of their goals (i.e., effectively cope with common problems and difficulties of goal implementation) is planning

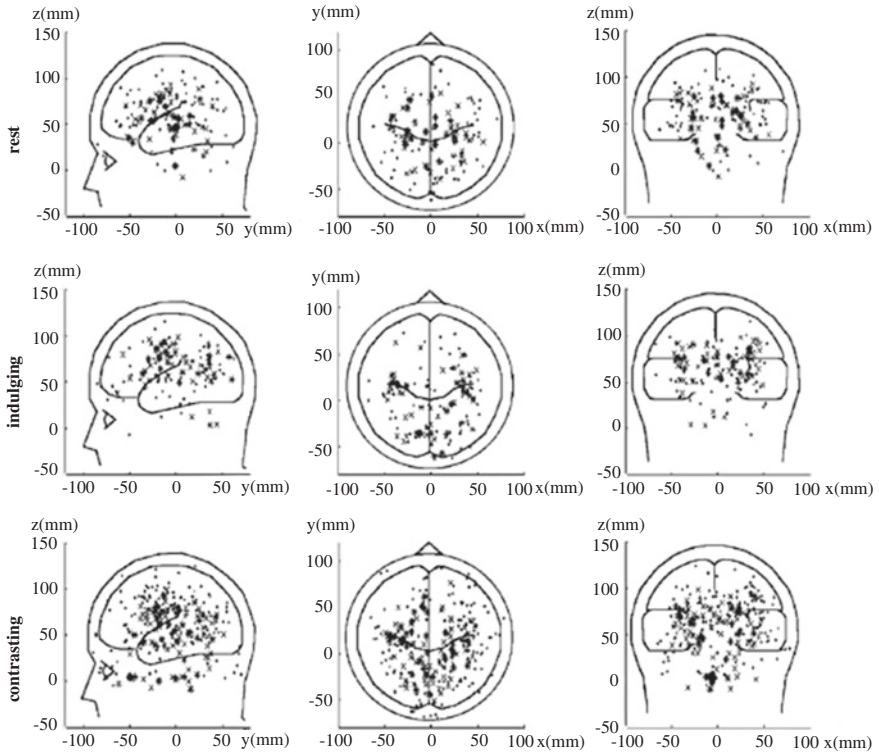

Fig. 2.1 Plotted multiple dipole density (MDD) over all participants for resting, indulging, and mental contrasting

out one's goal striving in advance via if-then plans or implementation intentions. Implementation intentions define when, where, and how one will act on one's goals (or goal intentions). Goal intentions have the structure of "I intend to reach Z!" as they merely specify a desired performance or outcome the individual feels committed to attain. Implementation intentions, on the contrary, have the structure of "If situation X is encountered, then I will perform the goal-directed response Y!", as they spell out how the goal intention will be realized once a goal-relevant situational cue is encountered. By forming implementation intentions, an anticipated critical situation is linked to a goal-directed response, and a commitment to respond to the specified critical situation in a planned, goal-directed manner is created. Whereas goal intentions only specify a desired future behavior or outcome the individual feels committed to attain, implementation intentions specify how this will have to be accomplished.

Goal intentions (e.g., "I want to reduce my alcohol consumption") have been found in a recent meta-analysis to account only for 28 % of the variance in behavior (which qualifies as a weak effect size; Sheeran 2002). A meta-analysis on the efficacy of implementation intentions (Gollwitzer 1993, 1999) has however revealed a medium to large effect size for implementation intentions with respect to the higher rate of goal attainment in comparison to acting on goal intentions alone (d =0.65; Gollwitzer and Sheeran 2006). Indeed, in domains where simple goal intentions are rather ineffective, implementation intentions are commonly observed to help people achieve their goals: eating a healthy diet (Adriaanse et al. 2011), reducing pregnancy risk (Martin et al. 2011), vaccinating (Milkman et al. 2011), regular taking of pills (Sheeran and Orbell 1999), or performing cervical smear tests (Sheeran and Orbell 2000).

Implementation Intention Effects and Processes

Forming implementation intentions facilitates goal attainment on the basis of psychological processes that relate to both the anticipated critical situation and the specified goal-directed response. More specifically, an increased mental accessibility of the situational cue (e.g., Parks-Stamm et al. 2007; Webb and Sheeran 2007) and the establishment of a strong cue-response link (Webb and Sheeran 2008) mediate implementation intention effects. This heightened mental activation (and thus accessibility) of the situational cue has been shown to allow for easy detection, effective recall, and a readiness to attend to the critical situation even if one is otherwise cognitively busy (e.g., Achtziger et al. 2012). Further, the strong cue-response links which are established when a person forms implementation intentions lead to an automatic initiation of the specified goal-directed response in the presence of the specified situational cue. Consequently, action initiation becomes immediate, efficient, and no longer needs a conscious intent (Bayer et al. 2009; Brandstätter et al. 2001; Gollwitzer and Brandstätter 1997).

Electrocortical Correlates of Implementation Intentions

Although the mechanisms underlying the effectiveness of implementation intentions have been studied for years using various cognitive task paradigms, little was known until recently about their underlying neural correlates. These correlates help to establish a deeper understanding of the temporal dynamics and attention mechanisms, as well as the spatial distribution of brain activity associated with action control by implementation intentions.

The electrocortical correlates underlying action control by implementation intentions have been tested so far with two populations who are known to have action control difficulties: children with attention deficit hyperactivity disorders (ADHD) and individuals with high spider fear. As children with attention deficit hyperactivity disorder are known to be impulsive, Paul et al. (2007) used a stop signal task to assess whether children with ADHD might profit from forming implementation intentions in order to achieve better executive control. Therefore, children diagnosed with ADHD and control children without ADHD received in a first session instructions on how to perform a classification task (i.e., classifying animals vs. vehicles by pressing respective buttons). Then, in the second session where the classification task was modified into a stop signal task, an implementation intention was established on how to deal with the stop signal that was presented for some of the classification trails ("If I see a stop sign, then I will not press any button"). In the second session of the classification task, animals and vehicles were presented and children were asked to respond to them as in the first session by pressing one of two buttons, respectively; however, they were asked to inhibit their responses when a stop signal appeared on the screen. Behavioral data supported the prediction of less inhibition errors to the stop signals in ADHD children after having formed an implementation intention, compared to children with ADHD who were only assigned the goal to refrain from showing a classification response when a stop signal was presented. Importantly, compared to the goal intention participants the implementation intention participants also showed an amplitude increase during the first half of the component known as P300 for the presented stop signals. Thus, children with ADHD in the goal intention condition showed the typically less pronounced amplitude increase in response to stop stimuli, whereas implementation intentions improved response inhibition and increased the P300 to the level of children without ADHD. As the P300 reflects the decision to withhold the execution of a motor response (Jackson et al. 1999), the finding that children with ADHD in the implementation intention condition improved their performance to the level of children without ADHD suggests that forming implementation intentions disencumber executive functions and thus facilitate action control.

Another study by Schweiger Gallo et al. (2009, Study 3) targeted a different population: people with high spider fear. Though participants with spider fear have been previously shown to be able to down-regulate their fear when they formed implementation intentions to keep calm and relaxed (Schweiger Gallo and

Gollwitzer 2007), it remained unclear what was responsible for these effects. In order to gain insights into the neurocortical correlates underlying the effectiveness of implementation intentions in emotion regulation, Schweiger Gallo et al. (2009) complemented self-report data with electrophysiological recordings in a study where the selected implementation intention focused on ignoring the spiders. Participants were assigned to a control (watch only) condition, a goal intention condition ("I will not get frightened!") or goal intention plus implementation intention condition ("And if I see a spider, then I will ignore it!"). All participants were then presented pleasant (for example, appetizing food) and neutral (for example, household objects) pictures, as well as spider pictures. In line with other studies on emotion regulation by implementation intentions (e.g., Schweiger Gallo et al. 2009, Studies 1 and 2), self-report data revealed that participants with an ignore-implementation intention were able to down-regulate their fear when looking at spiders. Importantly, no such differences were found for the experience of the pleasant and neutral pictures (i.e., implementation intention effects were only found for the specific fear-eliciting stimuli, which were discriminated from the pleasant and neutral stimuli). Electrophysiological recordings corroborated these results, as a differential activity in response to the spider slides was found in terms of a smaller P1 at right parietal and right occipital sites in implementation intention participants only. In contrast, both control and goal intention condition participants showed the typical positivity of the P1 after processing the unpleasant pictures. As the P1 is known to discriminate between affective stimulus content and larger P1 amplitudes are observed with unpleasant than pleasant or neutral pictures (see review by Olofsson et al. 2008), this finding suggests that implementation intentions produce their effects through cortical control that appears very early (i.e., at around 120 ms) in stimulus processing. Thus, ignore-implementation intentions do not appear to down-regulate an already experienced negative emotion, but rather block the emergence of negative emotions at their onset. In a later time segment, the slow wave at 550–750 ms, both self-regulatory conditions (i.e., goal intention and implementation intention participants) differed at right frontal sensors from the control condition. As the frontal slow wave has been related to prospective remembering (e.g., West et al. 2000), and as goal intentions and implementation intentions have been shown to rely on prospective memory processes (Gollwitzer and Cohen 2008), the results by Schweiger Gallo et al. (2009) imply that during this time window of 550–750 ms instructions are kept in mind and realized.

Neural Correlates of Implementation Intentions

Prospective memory focuses on the memory aspect of carrying out intentions: it is the ability to encode an intention and then successfully remember to execute it at the appropriate future moment (Einstein and McDaniel 1990). Einstein et al. (2005) have suggested that in some situations, prospective remembering can occur relatively

automatically, as a result of direct triggering by environmental stimuli. In other situations, prospective remembering may depend more heavily on deliberate monitoring of one's environment for target events (Smith, 2003). Einstein et al. (2005) suggested that the extent to which these different types of processes are engaged can depend on whether a good link was formed between an anticipated cue and the intended action. Parallel to this distinction, implementation intentions are thought to facilitate goal attainment because they specify a mandatory action when a particular cue is encountered. In contrast, a goal intention is more reliant on self-initiated behavior.

In recent years, neuroimaging studies have adopted prospective memory paradigms in order to specifically assess the spatial distribution of brain activity underlying the formation of implementation intentions. Previous cognitive neuroscience studies have highlighted the rostral prefrontal cortex (PFC), approximating Brodmann area 10 (BA 10), as an important region in prospective memory (Burgess et al. 2008). Neuroimaging studies typically show that performance of prospective memory tasks, compared with performance of ongoing tasks alone, elicit increased activity in lateral BA 10 and decreased activity in medial BA 10. Burgess and colleagues have accounted for these results by suggesting that lateral BA 10 plays a role in attending to internally represented information such as intentions for future action; hence the signal in this region is increased during prospective memory performance. In contrast, medial BA 10 is thought to play a role in attention toward perceptual information in tasks that can be performed on the basis of well-learned stimulus–response links (Burgess et al. 2007).

Experimental studies in cognitive neuroscience and psychology often fail to describe in precise detail the manner in which participants were instructed about the demands of a task. Subtle differences in the wording of task instructions can have significant consequences for task performance, however. In a study conducted by Gilbert et al. (2009), the authors used a modified prospective memory paradigm to examine the effects of task instructions on behavioral performance as well as the underlying brain activity. Participants were assigned to one of two conditions with different sets of instructions in each. In the goal intention condition participants acted on the following instructions: "In this part of the experiment, you must try to score as many points as possible." They were told that they would score 1 point for every ongoing trial (i.e., two letters were presented, one capitalized, and the participants had to indicate on which side the capitalized letter appeared) and 5 points if they pressed a prospective memory response key (the middle button on the keypad) when a prospective memory target was presented (i.e., the two presented letters were of the same kind, e.g., one was an "F" and the other an "f"). They were then asked to silently read an instruction phrase that extended the goal intention of making as many points as possible by using an if-then phrase that simply reminded of the reward contingencies relevant to the goal of making as many points as possible (e.g., in the letters task, "IF the same letter is on both sides, THEN I can score 5 points!"). In the implementation intention condition, however, participants were told to furnish the goal intention of making as many points as possible with an implementation intention that if a prospective memory target was presented, they will press the prospective memory

response key. The instruction phrase used in this condition was "IF the same letter is on both sides, THEN I will press the middle button!" The goal and implementation intention conditions were thus identical except that they differed in terms of what they focused on. In the goal intention condition, a link was made between the prospective memory cue and the rewards linked to successful responding, whereas in the IMP condition, a link was made between the prospective memory cue and the to be executed goal-directed response, as in previous investigations of implementation intentions (Gollwitzer and Sheeran 2006).

Participants were then presented with the same stimuli in both conditions, and the same responses were appropriate to both conditions. The reward structure in the goal intention condition made it clear that participants should respond to prospective memory targets, without stating it explicitly as in the implementation intention condition. Thus, participants in the goal intention condition had to establish a more self-initiated strategy for responding to the prospective memory targets relative to the implementation intention condition. The objective was to examine whether behavioral performance and underlying brain activity is affected if participants are presented with the option to act, compared to an instruction to act when cued. Although the conditions differed only in the wording of instructions, the two conditions were associated with differential patterns of activity in rostral PFC (BA 10). That is, responding to prospective memory targets in the goal intention condition was associated with greater bilateral activity in the lateral BA 10, whereas responding to prospective memory targets in the implementation intention condition was associated with greater bilateral activity in the medial BA 10. The difference in target-related activity between these two conditions in lateral BA 10 mirrored the behavioral difference between the conditions, with greater activity associated with poorer performance. The authors suggested that these results reflect differing demands for self-initiated versus externally cued behavior following different types of instruction, in line with the distinction between goal intentions and implementation intentions proposed by Gollwitzer (1999; recent review of implementation intentions research by Gollwitzer and Oettingen 2011).

In a recent study, Gilbert et al. (2012) showed that successful prospective memory performance was associated with greater similarity between patterns of activity at encoding and retrieval. That is, pattern similarity between encoding and retrieval was greater for prospective memory hits than baseline but not significantly different between prospective memory misses and baseline. These results are consistent with the possibility that similar brain activity between encoding and retrieval may be responsible for boosting recall of delayed intentions. Gilbert et al. (2012) suggest that forming an implementation intention involves thinking about a specific future cue that facilitates retrieval of an intention (e.g., "When I sit down in the restaurant tonight, then I will order a salad!"). By contrast, goal intentions are formed in the absence of such specific cues (e.g., "I intend to eat more healthily"). Given that imagining a particular situation can produce similar brain activity to actually being in that situation (e.g., Stokes et al. 2009), Gilbert et al. (2012) suggest that thinking about a specific cue when forming an intention tends to increase the similarity

between brain activity at encoding and retrieval and this could underlie at least part of the benefits of implementation intentions over goal intentions.

Future Prospects

Intention Formation in the Health Domain

In recent years, the strategies of mental contrasting (MC) and implementation intentions (II) have been combined in interventions (MCII) in order to improve people's daily lives by helping them in achieving their desired behavior change goals (Oettingen 2012; Oettingen and Gollwitzer 2010). Such desired behavior changes in the health domain include heightening one's physical activity, eating a healthy diet, or reducing the intake of unhealthy snacks—behaviors that have been shown to be difficult to change. By combining both strategies, the benefits of mental contrasting (fostering of strong goal commitments and energization) and implementation intentions (instigation of automatic action control) are united via a single self-regulation strategy.

In this vein, MCII has been shown to produce lasting behavior change effects. The temporal stability of MCII effects has been demonstrated in two studies by Stadler et al. (2009, 2010). In a first study, Stadler et al. (2009) analyzed the effects of two groups (a health information intervention only group and an information plus MCII intervention group) on the physical activity of a group of middle-aged women. Whereas women in the information-only control condition learned about the benefits of regular exercise, those in the MCII group received the same information and learned the mental contrasting with implementation intentions technique. Results across 4 months showed that the information plus MCII group was twice as physically active as the information-only group.

Integrating mental contrasting and implementation intentions, Stadler et al. (2010) also tested the effects of two interventions (i.e., information only vs. information plus MCII) on eating a healthy diet in women. Compared to the baseline, both groups ate more fruits and vegetables in the first month. However, two years later only information and self-regulation group participants ate healthier than participants in the information only group, who returned to their baseline level. The effects of a combined intervention have also been replicated for unhealthy snacking habits (Adriaanse et al. 2010): as in the previous studies, participants in the combined intervention group reported a greater reduction of their unhealthy snacking habit than control participants. Importantly, MCII also produced a greater reduction than both mental contrasting and implementation intentions alone.

MCII has also shown to be a powerful time- and cost-effective self-regulatory tool in a study involving chronic back pain patients (Christiansen et al. 2010). Results showed that the MCII intervention group increased physical strength and mobility at 10 days and 3 months after the intervention, as assessed by subjective and objective measures. Importantly, the intervention consisted only of two sessions for a total of 1 h; this certainly qualifies the MCII intervention as very time- and cost-effective.

Future Research on the Neurophysiological Correlates of the Self-Regulation of Goal Pursuit

Although the first steps have been taken so as to better understand the neurophysiological correlates of forming implementation intentions and engaging in mental contrasting as well as their consequences on action control, further studies are needed to arrive at a better understanding of these strategies. This includes, for example, complementing the existing studies on mental contrasting with electrophysiological and imaging data. Foremost, however, future research might especially benefit from analyzing the neurophysiological correlates underlying MCII effects. Despite being a powerful intervention tool that produces long-lasting changes, no studies have focused so far on the temporal and spatial brain correlates underlying the effectiveness of this self-regulatory tool. Thus, assessing which brain activity is associated with going through the mental exercise of MCII, as well as the brain activity implicated in acting on the basis of MCIIs, is intriguing, as is the question of whether people who adopt MCII as a general metacognitive strategy show different neurophysiological patterns when selecting and acting on goals as compared to people who do not habitually select and implement their goals on the basis of MCII reasoning. In all, we expect in the years to come a growing interest into the neurophysiological foundations of various self-regulatory strategies, including mental contrasting, implementation intentions, and MCII.

Highlights

- Successful goal striving requires that people choose adequate goals and cope effectively with challenges on the way to goal attainment. This can be facilitated by using the self-regulation strategies referred to as mental contrasting and forming implementation intentions.
- Continuous magnetoencephalography (MEG) data corroborate that mental contrasting is a purposeful problem-solving strategy that differs from merely indulging in a desired positive future.
- Electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) data support the assumption that by forming implementation intentions people switch from top-down control of their actions via goals to bottom-up control via specified situational stimuli, and thus confirm the postulate that action control by implementation intentions is based on strategic automaticity.
- The mental contrasting and forming implementation intentions have recently been integrated into one single, cost- and time-effective behavior change intervention called MCII that enhances healthy and prevents unhealthy behaviors.
- Self-regulation strategies of successful goal pursuit qualify as an important determinant of public health when they are used to reach one's health goals.

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Chapter 3
Temporal Self-Regulation Theory: Integrating Biological, Psychological, and Ecological Determinants of Health Behavior Performance

Peter A. Hall and Geoffrey T. Fong

Background

Understanding of causality is essential for planning interventions to influence the behaviors of individuals, special groups, and whole populations. For this reason, explanatory (i.e., causal) models for individual health behavior provide a strong foundation for public health practise. This is not to say that individual behavior is the only important determinant of health outcomes, or that all influences on behavior are within the mind of the individual; contextual forces are not only important influences on behavior, but in fact exist as very central ones. However, there are many points of intersection between individual behavior and contextual factors. For this reason, models of individual behavior must incorporate some points of interface with the ecological context, and ecological models must incorporate an understanding of individual behavior.

This being said, there are significant limitations of established models of individual health behavior, partially as a function of when they were developed. The most commonly used models of individual health behavior were conceived at a time when we knew relatively little about brain-behavior relationships (i.e., before the advent of functional neuroimaging techniques in behavioral research), and when our understanding of ecological influences on health behavior was in its infancy. Moreover, we now know that most of the older models do not account for as much variability in behavior as we might like; one of the major problems has been the assumption of uniformity regarding the intention-behavior relation, which is actually subject to several modifying factors (Webb and Sheeran 2006).

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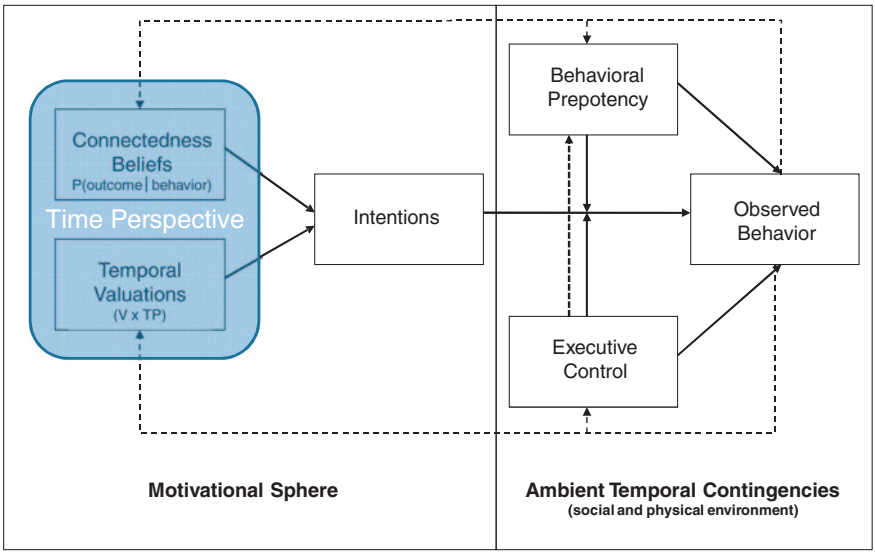

Fig. 3.1 Graphical representation of the TST model. *Note Arrows* between behavioral prepotency and executive control resources to the Intentions-*behavior arrow* implies moderation; $V =$ value; $TP =$ perceived temporal proximity. *Broken arrows* denote weaker (i.e., secondary) hypothesized effects. (Adapted from Hall and Fong 2007)

Temporal self-regulation theory (TST) is one of a class of new models that take into account brain-based control resources, the habitual nature of repeated behaviors, and self-regulatory demand imposed by the ecological context, when explaining variability in individual health behavior trajectories. The model is depicted in Fig. 3.1, and we describe each of its components below. We believe that it represents a significant increment over existing models because of these above features.

A Summary of the TST model

For the purposes of this chapter, we define the term "health behavior" as any behavior that is undertaken (intentionally or not) that has an acute or cumulative effect on the health status or disease risk of the individual. Such behaviors can be preventative in nature (i.e., healthy dietary choices, regular exercise, screening behaviors) or risk conferring in nature (i.e., substance abuse, risky driving, unsafe sexual practices). Health behaviors include both repetitive behaviors that can establish long-standing patterns (e.g., smoking behavior over several decades of life), or single occurrence behaviors (e.g., obtaining a blood test).

According to the TST model, health behaviors are thought to reflect the joint influence of three proximal factors: (1) intention strength, (2) executive control resource availability (i.e., inhibition, working memory and attentional set shifting), and (3) behavioral prepotency (i.e., the default status of the behavior). The TST model also includes the temporally proximal (i.e., immediate) and temporally distal (i.e., remote) influences of contingencies supplied by the ecological context in which the behavior occurs, and the time lagged nature of these. Specifically, it is assumed that contingencies are afforded more influence as they are more proximal in time to the point of behavioral execution, and that the value curve assumes a hyperbolic function, as is proposed by contemporary models of inter-temporal choice (Ainslie 2013).

Because ecological context (physical, social, systemic) is a primary determinant of what contingencies exist for a given health behavior and how close in time they fall in relation to behavior enactment, there is a fundamental connection between the behavior to be explained and its ecological context. Healthy behaviors with largely distal benefits rely more on habit support and executive control resources than those with relatively immediate benefits, when all other factors are equal. And so, broadly speaking, the ecological context—referred to in the model as *ambient temporal contingencies*—determines the relative causal influence of other variables in the model when explaining health behaviors. Upstream from intention are a number of other influences on behavior that transmit through intention, including the extent to which behaviors are viewed within a temporally proximal or temporally distal lens. Such influences can be captured pragmatically via the construct of *behavior-specific time perspective*, reflecting the tendency to attend to and value temporally proximal versus temporally distal outcomes of one's actions. Together, time perspective and intention constitute the *motivational sphere* of influences on behavior.

Like predecessors such as the Theory of Planned Behavior (Fishbein and Ajzen 2010), TST includes behavioral intention, such that intention is a central determinant of behavior. However, both prepotency and **executive control resources** (ECRs) moderate the intention-behavior link. Intentions are assumed to be more easily translatable into action among those with strong ECRs compared to weaker ECRs, and intention is likewise more influential when behavioral prepotency is low. Importantly, however, each of these variables (ECRs and prepotency) also exert a direct causal influence on behavior, that is, influence not mediated through intention. As such, frequently repeated behaviors that always occur in the same context are assumed to be performed as a function of habit strength, for example, in a relatively "automatic" fashion (i.e., without much mediation through intention); likewise, weak ECRs may make people more responsive to environmental cues to perform a behavior, regardless of intention and without mediation through intention.

Biological Facets of TST

Unlike pure social cognitive models such as the TPB, which can be tested in its entirety with self-report measures, it is not completely feasible to conduct a

complete and comprehensive test of the TST model in a single empirical study. Instead, individually testing components of the model is a better approach, and an approach that is much more consistent with complex theory in the life and physical sciences (and even some social sciences). Along these lines, there have been encouraging findings confirming several of the links proposed in the TST model and some of the general propositions. For example, using a prospective observational design, Hall and colleagues (Hall et al. 2008) demonstrated that those with stronger performance on a reaction time measure of ECRs showed stronger intention-behavior relationships over time for exercise and diet than those with weaker ECRs. In a follow-up study (Hall 2012b) using a community sample, participants completed measures of ECRs and consumption of appetitive but unhealthy fatty foods and were tracked over a two-week interval. Findings revealed that those with stronger ECRs consumed significantly fewer fatty foods, even though ECRs had no relationship to non-fatty foods. More recently, Nederkoorn et al. (2010) demonstrated that a combination of strong preferences for snack foods and weak inhibitory control predicted more BMI gain over the course of a 1-year follow-up interval.

Interestingly, the relationship between ECRs and health protective behaviors such as dietary behavior and physical activity also appears to be stronger (almost twice as strong in absolute terms; Hall and Fong 2013) than personality traits like conscientiousness that have previously been linked with health-related behaviors (Bogg and Roberts 2004). To date many investigations have implicated ECRs in the performance of health-related behaviors, via direct or indirect links (Becker et al. 2011; Ettenhofer et al. 2010; Hall et al. 2006; Hall 2012b; Hinkin et al. 2002; Insel et al. 2006; Jasinska et al. 2012; Panos et al. 2013), and some emerging literature supporting the causal status of such relationships in the dietary domain (e.g., Fregni et al. 2008; Houben and Jansen 2011).

It has further been demonstrated that individual differences in ECRs have substantial implications for the ultimate health outcome: longevity. In one study (Hall et al. 2009), we examined the extent to which individual differences in ECRs predict all-cause mortality among initially healthy older adults. Selecting only those older adults with no signs of chronic illness or cognitive decline at baseline, we found that a 1 *SD* increment in ECRs was associated with a 30 % reduction in mortality hazard over the 10-year follow-up; this trend remained strong after adjustment for demographics, and after removal of those who had died due to dementia or a related disease process. Moreover, an interesting trend emerged when we examined the sources of excess mortality—the excess risk conferred by low baseline performance on measures of ECRs appeared to be primarily attributable to a much higher rate of new onset of chronic illness among those with weaker ECRs: about 53 % of those with strong ECRs had died from a chronic illness at follow-up, compared to 78 % of those with weak ECRs. The latter is particularly interesting given that risk for chronic illnesses is known to be accentuated by poor behavioral patterns. Interestingly, there have been a few other studies providing replication of these effects of ECRs on longevity in other datasets (Duff et al. 2009). A more recent study by another group of investigators compared

those individuals with demonstrated exceptional survival with controls, and found that the two groups were differentiated based on performance on cognitive tasks that are heavily loaded with executive control requirements (Barral et al. 2012). This investigation used data from the long life family study (LLFS) to compare probands and their siblings who had come from families with exceptionally long life expectancy to a control group (their spouses). They administered cognitive performance measures to both groups, and compared them based on scores. They found that the probands and siblings from families with demonstrated longevity had higher scores on digits forward, digits backward, and one of two verbal fluency tasks. The differences between groups on cognitive tasks were selective to these tests but not others (i.e., logical memory).

Finally, it is possible that ECRs also predict survival time among those living with one of these same chronic illnesses as they carry significant self-care demands; we found support for this contention as well (see Fig. 3.2; Hall et al. 2010). Using a sample of older adults who had one of three chronic illnesses at baseline, we found that ECRs reliably predicted survival time even when accounting for covariates, but global cognition did not. The significance of this finding on a theoretical level is substantial, because all three conditions (diabetes, cardiovascular disorders, and neoplasms) carry significant behavioural self-management demands, and survival time is known to be dependent on these. Moreover, the effect of ECRs on survival time did not vary significantly by disease category, so it is reasonable to conclude that ECRs exert a relatively uniform effect on survival in the context of chronic

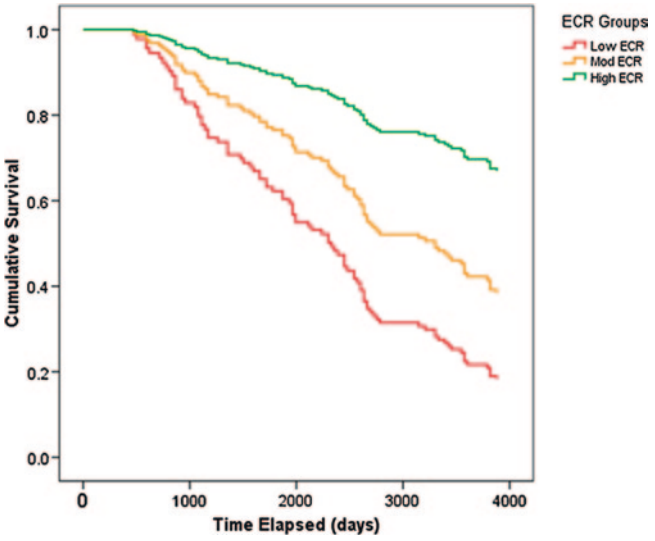

Fig. 3.2 Survival time for chronic illnesses with heavy self-management demands as a function of ECR category. *Note* Log-Rank Test: $\chi^2 = 21.245$ ($p < 0.001$); time elapsed is in days; *y*-axis indicates survival probability; *x*-axis indicates survival time in days. Reprinted with permission from Hall et al. (2010)

illnesses that carry heavy self-management demands. Interestingly, we did not find similar effects for infectious illnesses, suggesting that this is an effect that is unique to chronic illness.

Together these findings suggest that stronger ECRs are associated with greater longevity, and may in fact serve as an endophenotype for longevity. Given the substantial heritability demonstrated for individual differences in ECRs in some studies (Friedman et al. 2008), this could be an important finding. This should not be taken to mean that ECRs are not malleable, given that the genetic aspect includes gene x environment interactions. The possibility that ECRs can be influenced by momentary factors (i.e., sleep deprivation, stimulant ingestion, acute exercise) remains, even though the rank ordering of ECRs in the general population would remain the same given the presence of similar momentary influences. To illustrate this, take for example two purely hypothetical individuals, one who has an ECR score of 8.5 on an arbitrary scale of 1–10 (Person A), and the other who has a score of 7.0 out of 10 (Person B). If, on one day, Person A experiences extreme sleep deprivation, her ECR performance on the subsequent day may drop to 6.5 temporarily. Person B, who was not sleep-deprived, would maintain her score of 7.0, thereby outperforming Person A. That is, a temporary factor served to modulate ECR ability in Person A relative to Person B, leaving Person B at an advantage (though this would not normally be the case). However, if we were to expose both Person B and Person A to similar degrees of sleep deprivation, Person B may drop to 5.0 while Person A might only drop to 6.5. As such, under similar conditions, the rank order is retained. Importantly, one is partially in control of one's environmental influences: one can exercise more, get sufficient sleep, and hopefully ingest moderate amounts of caffeine to offset fatigue when necessary. Each of these could boost ECRs temporarily, or help to preserve them. So, although individual differences in ECRs may be highly genetically determined, momentary fluctuations are still meaningful. Moreover part of the heritability estimate actually includes gene x environment transactions that could involve exposure to ECR-modulating conditions.

The Biological Basis of Control: One System or Two?

Several models of human choice behavior make compatible claims about the determinants of health-related behaviors. For example, Hofmann's model (Hofmann et al. 2008) posits the existence of separable control systems (the "reflective system") and impulsive systems (the "reflexive system") whose interaction produces behavioral tendencies. Such two-system theorizing maps neatly onto several other major theoretical approaches to human behavior, including Michel's "hot" and "cool" systems, as well as McClure and colleagues' Alpha and Beta systems (McClure et al. 2004). So, the dual systems approach is easily digestible within the realm of personality and social psychology, and has been very influential in these areas as a result. There are strong connections between such theorizing and the notion of self-regulation, and associated brain-based cognitive processing postulated by TST (see Hofmann et al. 2012 for a review).

The central question in relation to TST, however, is as follows: does such dual system modeling improve on the TST model by incorporating two interacting systems rather than one single control system (i.e., executive control)? In fact, the answer is complex, and is probably not one that can be determined by competitive model-fitting (even if one could return to the days of testing an entire health behavior model with a single study). On a theoretical level, the existence of a second "impulsive" system is entirely consistent with TST in that such reflexive tendencies are part of the *behavioral prepotency* construct. For instance, presenting food to a hungry individual is likely to increase the probability of consumption, even in the presence of intended restraint. However, even this scenario does not include all of the possible influences on prepotency, as they might also include the presence of others and social pressure to restrain one's self. These latter factors all fall into the determinants of *behavioral prepotency*, and so reflexive (or visceral) factors are combined with social factors to determine a given behavior's "default" status (note that the visceral factors are not, however, given any inherent prominence over social factors). In summary, TST would not be reducible to a "two-system" or "duel-systems" model because it includes more than simply two interacting systems; on the other hand, TST is entirely *consistent* with the existence of two interacting systems (so long as we consider more than only those two systems).

Psychological Facets of TST

A further empirical link in the causal chain of the TST model that has been investigated is the link between *time perspective* and behavior, as mediated through intention. Time perspective can be defined as the extent to which someone values and attends to short- versus long-term consequences of a particular behavior. Time perspective is a pragmatic placeholder for what is actually a more complex set of variables that were part of the original articulation of the TST model (Hall and Fong 2007). In the original model, expectancies about individual behavioural contingencies and associated values attached to them (modified by temporal proximity of each) comprise the primary determinants of behavioral intention. With the understanding that measurement of the constructs needs to be at least somewhat simplified to facilitate design of intervention strategies among practitioners and public health researchers, this set of constructs was replaced with the individual difference variable of time perspective, which approximates the balance of connectedness beliefs and temporal valuations for any given target behavior. What we gain in feasibility we lose in precision, but ultimately either version of the model (either the original or simplified model) may be tested/applied, depending on the needs of the investigator or intervention strategist.

To date there have been many studies linking a stronger future orientation with more consistent performance of health protective behaviors and/or avoidance of health risk behaviors (Adams 2009a, b; Adams and Nettle 2009; Adams and

White 2009; Hall and Epp 2013; Hall and Fong 2003; Henson et al. 2006; Keough et al. 1999; Rothspan and Read 1996; Wills et al. 2001; Zimbardo and Boyd 1999). To date only two studies—both conducted by ourselves and our colleagues—have examined the mediational status of the relation between future orientation and health behavior. In the first, we examined the association between time perspective and uptake of weight management behaviors (exercise and avoidance of fatty foods) among those newly diagnosed with Type 2 diabetes over a 6-month period (T2DM; Hall et al. 2012a). We utilized bootstrapping procedures to quantify the indirect effect of time perspective on behavior as mediated through intention strength, and found support for the mediational model for both behaviors (Figs. 3.3 and 3.4). In a second study, we examined the extent to which time perspective predicted quitting behavior among current smokers as mediated by intention strength (Hall et al. 2012b; Fig. 3.5). Again, this time using multiple mediation procedures, we found that intention was the most important mediator of the relationship

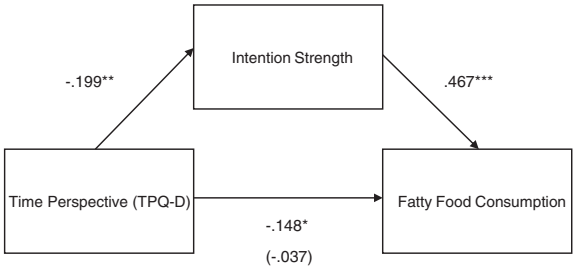

Fig. 3.3 Mediational model for fatty food consumption. *Note* $N = 204$; *TPQ-D* = time perspective questionnaire, dietary version; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$; control variables: baseline dietary behavior, demographics (age, gender, socioeconomic status, relationship status), body mass index and disease variables (time since diagnosis, history of gestational diabetes and/or impaired glucose tolerance). Coefficients are standardized beta weights; attenuated coefficients are presented in parentheses. (Adapted from Hall et al. 2012a)

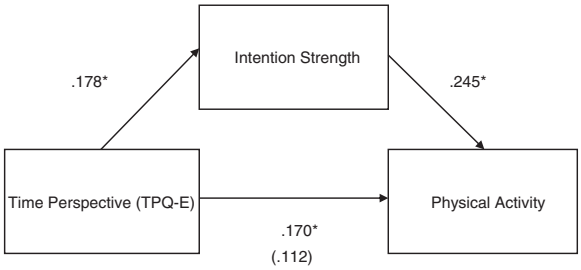

Fig. 3.4 Mediational model for physical activity. *Note* $N = 204$; *TPQ-E* = time perspective questionnaire, exercise version; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$; control variables: baseline physical activity, demographics (age, gender, socioeconomic status, relationship status), body mass index and disease variables (time since diagnosis, history of gestational diabetes and/or impaired glucose tolerance). Coefficients are standardized beta weights; attenuated coefficients are presented in parentheses. (Adapted from Hall et al. 2012a)

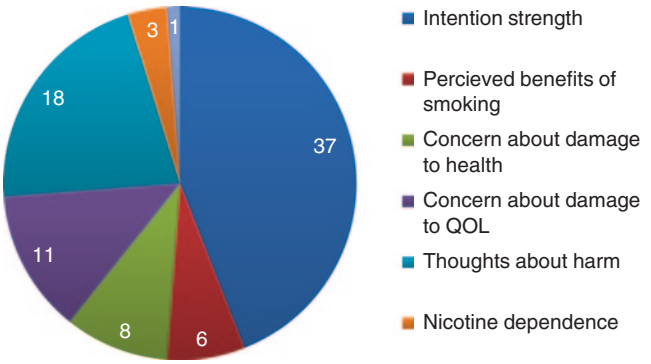

Fig. 3.5 Mediation (%) of time perspective effects on quit attempts (Hall et al. 2012b)

between time perspective and quitting attempt frequency among current smokers across four countries and almost 10,000 respondents.

One final construct in the TST model from the psychological sphere is *behavioral prepotency*. Behavioral prepotency can be operationalized as the amount of psychological inertia a behavior is imbued with (Hall and Fong 2007). Prepotency is proportional to the sheer frequency of past performance (i.e., past behavior) in a stable context, the presence of strong cues to action, or the similarity of the behavior to that of others in the immediate social context. When interpreting behavioral prepotency in relation to frequency of past performance, the construct has much in common with habit strength. Prior findings have linked this facet of prepotency—habit strength—with a number of important health behaviors, and past behavior itself is one of the strongest predictors of future behavior in the health domain and outside of it (Wood and Neal 2007).

Ecological Facets of TST

Ambient temporal contingencies are an important link between individual and ecological contexts in the TST model. The ecological context is crucial when considering causal influences on health behavior. This is true not only from the perspective of internally perceived rewards and punishments, but from the perspective of social, political, and even physical pressures exerted on the individual. Such contingencies are at once both multi-layered, and temporally complex (Ainslie 2013). Consider the case of exercise. What would be the self-regulatory cost associated with walking down the street to attend a well-appointed fitness facility complete with a baby minding service for a wealthy married mother of one? How would this compare to a single mom who has to travel across town and find child minding services on her own because her modest fitness facility has no

such services? Even when removing the monetary cost from the situation, the time cost to the wealthy female is only the time of the workout plus five minutes or so to find her bag, and walk down the block and drop off her child at the door. The less well-to-do mother, on the other hand, may have a 45-min bus ride, 10-min wait for the bus (i.e., almost an hour of transportation time in each direction), plus the time required for the workout itself. This is how socioeconomic status can have an impact on self-regulatory success, even without directly affecting monetary cost. Although it is technically possible for each mother to engage in a session of exercise in that day, the time cost to the privileged mother would likely be considerably less than that of the less-advantaged mother. Such asymmetries imposed by contextual factors (like SES and physical environment) are only given very indirect consideration in existing models of health behavior. However, in TST it is possible to model them rather directly, as they form some of the ambient temporal contingencies that invoke the need for self-regulatory resources, and/or support or reduce the prepotency of a given behavior (both of which are moderators of the intention-behavior link, a topic that we turn to next in more detail).

One of the centrally important facets of TST is modeling of the interface between the individual and their environment. The reason for this is not only to account for behavioral contingencies (punishments, reinforcements) but also to account for the primacy of the environment in providing a time course for all of these. We know from extensive research and theorizing in behavioral decision making that immediate consequences are disproportionately influential on behavior relative to more temporally removed consequences. That is, although one might (in theory) value an extra 7 years of life much more than one might value freedom from withdrawal symptoms that might accompany the decision to forgo the next cigarette, the relative influence of each on behavior switches dramatically as the choice point is reached. Put differently, the potency of an outcome changes as the choice point becomes more proximal. Ainslie (2013) has documented, for example, that when two rewards are removed in time, one might value reward A over reward B, but when reward B is imminently available, it may in fact be chosen over reward A (if reward A is not yet imminently available). These can be thought of as the temporal mechanics of failure to delay gratification (e.g., Mischel et al. 1989).

There is also a reasonable interface between TST and how behavioral economists conceptualize brain and behavior in economic choice theory. For instance, “Cool” brain systems—which are fundamentally abstract, intellectual, and generally non-visceral—are invoked in deciding between two rewards which are not immediately available, but when one reward is present or very near in time, the “hot” brain systems—concrete, feeling-based, and highly visceral—are activated. This scenario results in a conflict between “hot” and “cool” systems, which, more often than not, leads to the “hot” system winning. When we see the disappointing data regarding people’s ability to resist rewarding foods, inability to desist from substance use, despite truthfully articulated intentions to do so, we should keep these dynamics in mind. At the very least, one might have appreciation for why one may state that they want to do something, and yet not follow through on it when the choice point is reached.

However, the main point here is that temporal asymmetries for behavioral contingencies exist, and they exist partially because of the inherent qualities of health behaviors, and partially because of the potentially malleable qualities of the environments in which they are performed. For example, the decision to be physically active in daily life may be relatively easy to enact consistently in walking-friendly communities (i.e., those with good infrastructure for walking and active transit) and for individuals who do not have competing responsibilities (i.e., children to care for, medical conditions that impair mobility and/or limit independence). We should be especially concerned about the environmental sources of unfavorable temporal contingencies because they are potentially avoidable, or at least amenable to some remediation. That is, if we construct neighborhoods with walking and activity in mind (rather than, driving, for example) we may see less conflict between hot and cool systems when making the decision to walk. It may therefore enable people to make freer choices about their activity level than is currently the case.

How do we improve the temporal contingency profile for healthy behaviors? This should be one of the central questions for public health scientists to tackle. Although many attempts to improve availability of foods, walkability of neighborhoods, and access to care have existed for a long time, we have rarely discussed these in terms of contingency profiles within a temporal frame, at least in a systematic way. Ecological factors are not only about considering the different spheres of influence on behavior (Bronfrenbrenner 1979). This must be the most rudimentary and elementary starting point, but more work needs to be done to integrate the individual and their ecological context in a more systematic way. Modeling of ecological considerations within the TST model is an initial attempt to accomplish this.

Measuring the Constructs

In addition to specifying the nature of the theory itself, it is also helpful to give some guidance as to how each of the constructs within the theory are to be measured. Below we discuss each of the constructs in relation to measurement issues:

Executive Control Resources: Executive control resources (ECRs) can be measured with many standard measures of executive function, including neuropsychological tests as well as computer-administered paradigms used in the cognitive science literature. However, the choice of the specific test should depend on which facet of executive control is of interest. Although there are multiple ways of conceptualizing executive function, it is generally agreed that it is reducible to at least three sub-facets: inhibition, working memory, and set switching (Miyake and Friedman 2012). Tests of inhibition include the Stroop (Stroop 1935), Go/NoGo, and Stop signal (Logan 1994) paradigms. Working memory tests include N-back, Digits forward/backwards, and some variants of "dual task" paradigms. Tests of shifting include Global–local tasks, Number–letter, and Plus–minus paradigms (see Miyake et al. 2000 for descriptions). Finally, tests of complex ECRs (i.e., including prominent elements of inhibition, working memory and shifting) include

the Wisconsin Card Sort (Kimberg and Farah 1993), Tower of Hanoi (Humes et al. 1997) and the Iowa Gambling Task (Becharra et al. 1994). The administration of most of the above tests can be accomplished by the use of computer, though some also have pen and paper counterparts. There are a few self-report measures of executive function (or dysfunction) though these tend to be utilized more for children than for adults (an example is the Behavior Rating Scale for Executive function; Gerard et al. 2000). Given the multifaceted nature of ECRs, it might be tempting to pick the most available test at hand, however, thus far inhibition and working memory tests have the most well demonstrated associations with health-related behaviors to date, while shifting and complex ECRs tasks have shown less predictive power. The selection of working memory versus inhibition should be made based on theoretical considerations around what should be most relevant to the selected behavior in question.

Any of the above tests—or adapted versions of them—can be used in combination with functional neuroimaging techniques to examine degree of activation in areas of the brain that might be responsible for ECRs (including the prefrontal cortex, most centrally). There are a few such studies in existence, though generally the logistics associated with fMRI and EEG preclude large samples, and this is unlikely to change in the near future. However, such tools have been used with great success in the domain of health communication, in order to track the degree of engagement of attentional centers by health communication efforts (see Cascio et al. 2013 in this volume, as well as the seminal work by Langleblen et al. 2009). In addition, some use has been made of Transcranial Magnetic Stimulation (TMS) to actually manipulate ECRs (rather than just measure them) and observe subsequent effects on health-related cognitions and behavior; some of these studies are described in the corresponding chapter of this volume by Lowe and Hall (2013).

Behavioral prepotency: Behavioral prepotency is potentially quite complex to assess, and is highly idiosyncratic to the behavior and the specific context in which it is performed. The complexity lies partially in the fact that behavioral prepotency includes not only the frequency of past performance and habit strength, but also social norms, and the presence of cues to action (i.e., anything that influences the "default" status of the behavior in question). For pragmatic purposes a measure of habit strength or a report of past behavior can serve as a proxy in some cases. Self-report can be used for both of the latter, with Verplanken & Orbell's Habit Strength Index being the most well-known and well-validated measure (Verplanken and Orbell 2003). A simple measure of frequency of past performance of the behavior may suffice for large population surveys that seek to use TST constructs to predict health behaviors. Laboratory studies that have the luxury of more stringent measurement could make use of additional measures of cue saturation in the environment, or actually manipulate such cues, if the research protocol is experimental in nature.

Time perspective: Generally time perspective is measured by self-report inventory, and there are several available (Strathman et al. 1994; Fong and Hall 2003; Zimbardo and Boyd 1999). However, many measures are domain-general, in that they don't assess future-oriented thinking about any specific target behavior. We have found in several studies that future-oriented thinking is fairly behavior-specific and

behavior-specific measures of time perspective out predict domain-general versions, sometimes by a wide margin (e.g., Hall et al. 2012b; Hall and Epp 2013). Several behavior-specific measures are available, two of which are already published (exercise and dietary versions are available in the appendices of Hall et al. 2012a) and two additional versions appear below in the Appendix of this chapter; one for alcohol consumption (Appendix A) and the other for smoking behavior (Appendix B).

Intention strength: Strength of intention may be measured by any of the methods that are currently established for existing social cognitive models (i.e., TRA, TPB; Fishbein et al. 2010). It is recommended that, when possible, the measure be constructed to specify the nature of the behavior in detail, and the time window for execution. For example, "I intend to eat three servings of vegetables three times per day for the next 5 days" is superior to "I intend to improve my eating habits."

Epistemic Concerns

Social science and natural science are strange bedfellows, which historically has discouraged attempts to bridge the rather large chasm between the two. One of the sources of discomfort among social scientists has been the reductionism of the natural sciences, which at its worst can render the social and cognitive constructions upon which their fields are based declared not "real" because they are not directly observable. The natural sciences, on the other hand, at times have been distinctly uncomfortable with the rococo qualities of social science theory, and the field's variable fidelity to the scientific method. Due to the long history of estrangement, the first bridges between social and natural science were tenuous, and at times not structurally sound. More recent attempts—some in the health sciences—have been much more encouraging, but the path is still fraught with missteps and moments of reticence.

The applied field of public health finds itself squarely in the middle of the social and natural science perspectives, and seems to simultaneously reject reductionism and reject "frilly" theoretical perspectives. At worst, if carried too far, this could leave an intellectual void that is filled by "practise only" perspectives that render public health intervention nothing more than the most costly (in all senses) trial-and-error game in the history of organized health promotion. For an example of how costly well-intentioned trial and error can be—even when executed from a natural science perspective—see Pepin's (2011) rigorous and insightful review of the early beginnings of the AIDS epidemic in Africa, which are potentially traceable to public health efforts to eradicate tropical diseases through inoculation in the middle of the last century.

This precious middle ground between social and natural sciences is where the most important theory and research will emerge for the field of public health. If there is not a point when we can replace the models and perspectives articulated in this book with updated versions, we should be collectively worried, as it would be a sign of lack of incrementality. We sincerely hope that our grandchildren's

generation are not coping with the same problems from the same perspectives 100 years later, but instead have new approaches and technologies that build on what has been initiated previously.

Conclusions and Recommendations

Our understanding of the neurobiology of self-control and the complexities of ecological context impel changes in how we think about the causal determinants of health behavior. Recent theoretical and empirical developments suggest the need for integration of both these factors in realistic models that can inform public health practise and health promotion.

Identifying accurate causal models of health behavior is not solely an academic matter. Knowing about the causal determinants of health behaviors is a necessary precondition for influencing them systematically. Systematic approaches based on scientific knowledge are ultimately superior to trial and error, which is an approach that is much too costly and inefficient for any developed nation, and even more so for developing nations. As such, there is always need for close connection between policy, health promotion efforts, and the basic science of human behavior. Likewise, fully appropriate models (with sufficient complexity) depend on attention to the temporally dynamic nature of behavioral contingencies when considered in ecological, social, and political contexts. Familiarity with the latter, then, is vital and will not emerge from sitting in one's laboratory.

Applying the TST model can generate these general maxims regarding health promotion:

1. *Increase self-regulatory demand for undesired behaviors*: This can include increasing inconvenience or cost associated with the behavior in question. For example, if we decided as a society that we wanted to seriously reduce the consumption of unhealthy foods, we would reduce the ease of access to it (relative to healthy alternatives), and increase the monetary cost associated with purchasing it. This does not mean eliminating access, only making it relatively less convenient, more time-consuming, or otherwise resource intensive to access.
2. *Decrease self-regulatory demand for desired behaviors*: Reduction of the difficulty with which people engage in physical activity as part of everyday life, would be an example of this approach. And it is one that has been used with some success already in the active living approach to physical activity promotion. Enhancing convenience and reducing monetary cost are key.
3. *Optimize executive control resources*: Reliable enactment of behaviors requires optimal functioning of the brain regions that support goal-directed behavior. To date there is substantial evidence that aerobic activity (either in acute bouts or long-term training) can enhance cognitive performance across the lifespan, and specifically improve function of the prefrontal areas of the cortex (see McAuley et al. 2013 for a review); moreover, accumulating evidence suggests that resistance training may be of benefit as well (see Liu-Ambrose and Nagamatsu 2013, this volume). As such,

the addition of exercise to any behavior change attempt is useful on an individual level, as would be population-wide recommendations to keep active for the sake of preserving brain health. Beyond this, avoidance of activities and substances that impair prefrontal function would be useful as well, including avoidance of sleep deprivation, reduction of stress, and avoidance of excessive alcohol consumption.

4. *Enhance intention strength by encouraging future orientation:* For many health behaviors a focus on the here-and-now can reduce motivation to perform them, and overcoming this is necessary in order to mobilize the individual. Reminding the individual of non-immediate contingencies at crucial choice points (i.e., lighting up a cigarette, or making a meal choice) can help to retain future-oriented focus in decision making. However, such approaches should not be undertaken blindly. For example, Gallo et al. (2013) in this volume describe the importance of encouraging the juxtaposition of present state with desired future outcomes (i.e., mental contrasting) coupled with concrete behavioral plans for enabling action-oriented goal striving. As in life, the devil is in the details when systematic approaches to health promotion are concerned.
5. *Alter prepotency in strategic ways:* Reduce prepotency for undesired behaviors by changing features of the environment that cue the behavior, alter social norms for the behavior. Likewise, increasing prepotency of desirable health behaviors can be accomplished by saturating the environment with behavior-relevant cues, making environmental characteristics similar in settings where the behavior is desired, and making communications about normative information that might support the behavior.

Policy has an important role in almost all of these recommendations. For example, policy around environment structure can increase or decrease the ease of implementation of healthy behaviors, could encourage living conditions that maximize control resources, and enhance attention to long-term contingencies at important choice points. There are already many examples of policies that do exactly these things, though coordination of each of these approaches could be improved by using a theoretical understanding of behavior to guide such interventions.

Highlights

- Temporal self-regulation theory (TST) is a model of individual health behavior that incorporates cognitive resources and ecological factors.
- TST posits that intention is a proximal predictor of behavior, but its influence is modulated by executive control resources and behavioral prepotency.
- Temporal proximity of behavioral contingencies determines the need for self-regulatory resources, and the relative influence of prepotency.
- In accordance with TST, public health initiatives will stand the best chance of success if they accomplish the following: support prepotency through strategic behavior cueing, encourage optimization of cognitive control resources, and systematically engineer social and physical environments to support desired behaviors.

Appendix A

Time Perspective Questionnaire-Alcohol Version (TPQ-A)
Consider each of the statements below. For each, indicate your level of agreement or disagreement by using the following scale.

1	2	3	4	5	6	7
Disagree very strongly	Disagree strongly	Disagree	Neutral	Agree	Agree strongly	Agree very strongly

1.	Long-term sobriety is at least as important to me as the immediate pleasures of having a drink (e.g., getting a "buzz", relaxation)
2.	I do not spend much time thinking about my long-term sobriety plans
3.	I have a good sense of how I can cut down my drinking now and in the future
4.	I spend a great deal of time thinking about how my present drinking habits will affect my life later on
5.	I never consider the long-term consequences of drinking when I decide to have a drink
6.	I do not have long-term sobriety plans

Appendix B

Time Perspective Questionnaire-Smoking Version (TPQ-S)
Consider each of the statements below. For each, indicate your level of agreement or disagreement by using the following scale.

1	2	3	4	5	6	7
Disagree very strongly	Disagree strongly	Disagree	Neutral	Agree	Agree strongly	Agree very strongly

1.	Long-term quitting plans are at least as important to me as the immediate benefits of smoking (e.g., reduced craving, relaxation)
2.	I do not spend much time thinking about my long-term quitting plans
3.	I have a good sense of how I can cut down my smoking now and in the future
4.	I spend a great deal of time thinking about how my present smoking habits will affect my life later on
5.	I never consider the long-term consequences of smoking when I light up
6.	I do not have a long-term quit plan for smoking

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Part II
Health Communication

Chapter 4
Health Communications: Predicting Behavior Change from the Brain

Christopher N. Cascio, Sonya Dal Cin and Emily B. Falk

Introduction

Factors influencing people's health behaviors are multiple and complex. Both individual differences and environmental influences interact to influence behavior. Approaches to influencing health behaviors in the public sphere vary, ranging from physician advice to tax incentives. In addition, one prominent tool in the public health toolkit is the delivery of persuasive health messages via the mass media. Understanding how health communications influence behaviors has been a significant goal for researchers across a wide range of disciplines. In this chapter, we discuss how social neuroscience, and the emerging subfield of communication neuroscience, contribute to our understanding of the effects of health communications. We focus particularly on how neuroscience evidence pertaining to attitudes, persuasion, social influence, and behavior change can help bridge gaps in knowledge in ways that are not readily apparent through traditional methodological approaches. In addition, this chapter discusses future directions and methodological considerations that should be made when integrating neuroimaging methodology to aid in our understanding of health communications.

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Social Theories

Our understanding of the effects of health communications and social influence on health behavior is informed by a long history of research on persuasion (Petty and Cacioppo 1986), conformity and compliance (Asch 1955; Deutsch and Gerard 1955), and socialization (Glanz 2008). Major social theories of persuasive message processing have integrated many important advances from the past century, pointing to message, recipient, and communicator effects that moderate persuasive communications (Allport 1935; Hovland 1949; Lazarsfeld et al. 1948; Petty and Cacioppo 1986).

One difficulty in predicting health behavior change, however, is the uncertainty in knowing who will successfully traverse the gap between attitudes, intentions, and behavior. A number of mature theories including Health Belief Model (Becker 1974; Rosenstock 1974; Rosenstock et al. 1988), Health Action Process Approach (Lippke et al. 2004; Schwarzer 2008; Sniehotta et al. 2005), Theory of Reasoned Action (Ajzen and Fishbein 1980), Theory of Planned Behavior (Ajzen 1985), and Social Cognitive Theory (Bandura 1989, 2004) provide a framework for linking constructs such as attitudes, intentions, social norms, and self-efficacy to behavior change.

Despite considerable theoretical advancement in the past century, predicting attitude and behavior change in response to persuasive message exposure remains a difficult task (Armitage and Conner 2001). Our current understanding of behavior change relies heavily on self-reports (Araujo-Soares et al. 2009; Cowell, Farrelly et al. 2009; Hagger et al. 2002; Skar et al. 2008; Webb and Sheeran 2006), but self-reports of attitudes, intentions, personality characteristics, and predicted social influence do not fully predict future behavior change. A meta-analysis examining the relationship between behavior and intentions found that large changes in intentions only translate to small to medium changes in behavior (Webb and Sheeran 2006). Although self-report provides valuable information concerning behavior, there remains a large portion of variance unexplained. This may be a function of participants giving socially desirable answers (Booth-Kewley et al. 2007), unconscious influences (Wilson and Nisbett 1978), or a disconnect between responses given in a laboratory setting and the mental processes that take place in the real world (Glassman and Hadad 2006; Klesges et al. 1995).

Neuroimaging

Knowledge gained from neuroimaging may complement what we know from self-reports about how people process persuasive messages. In turn, gaining a firmer grasp on these underlying neural mechanisms can enable scientists to more accurately predict future behaviors. Imaging techniques, including functional magnetic resonance imaging (fMRI), functional near infrared spectroscopy (fNIRS), and electroencephalography (EEG) have given scientists the ability to observe neural responses to persuasive messages in real time, without imposing the concurrent cognitive task of asking participants to self-report on how they are processing messages

(Falk 2010). As such, these techniques may provide useful insight into the mechanisms involved in persuasion. They may also offer a promising addition to current methodologies used to predict behavior change in response to persuasive messages, such as health communications. However, it is important to note that although neuroimaging may provide unique insight into psychological processes, it has limitations (Poldrack 2006, 2008). Thus, neuroimaging is not a replacement for existing methodologies; we have the most to gain when multiple techniques are combined to understand behavior (Fig. 1) (Berkman and Falk 2013). A full review of brain regions and their function in social contexts is beyond the scope of this chapter. For those who are interested in a more comprehensive review of these topics, the following readings are suggested (Cabeza and Nyberg 2000; Lieberman 2010).

Attitudes

Attitudes are individuals' evaluations of ideas, people, or messages within their environment and are often related to behaviors (Zimbardo and Leippe 1991). A large body of literature has characterized neural correlates of attitudinal processes, including intergroup evaluations (Amodio et al. 2008) and motivational goals (Cunningham et al. 2008). Neuroimaging findings demonstrate the complex cognitive processes that contribute to attitude change and maintenance. For example, neural networks work together, integrating new and old information in order to make evaluations and generate attitudes (Cunningham et al. 2007). The Iterative Reprocessing (IR) Model captures the complex interplay of neural networks involved in evaluative processes and offers a framework for integrating our understanding of how implicit and explicit cues come together to arrive at attitudinal judgments (Cunningham et al. 2007). The development of such neurocognitive models may provide a more complete and accurate understanding of attitudes.

Changing one's attitude often starts with an initial struggle between old habits or views and new goals or information, which is likely to produce

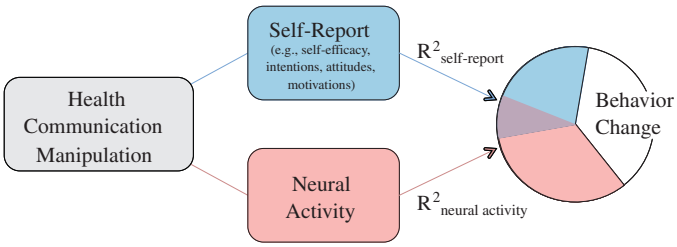

Fig. 1 Hypothetical model demonstrating the use of multiple methodologies to understand unique variance in behavior change in response to a health communication manipulation

dissonance. Dissonance refers to the anxiety produced from competing cognitions (Festinger 1957). Neuroimaging studies examining cognitive dissonance have found that increased activation of dorsal anterior cingulate cortex (dACC) and anterior insula (AI) are successfully associated with future attitude change (Jarcho et al. 2011; van Veen et al. 2009). These regions have been associated with conflict detection and negative affect, respectively (Carter and van Veen 2007; Lieberman et al. 2007). One interpretation of these data is that increases in negative affect resulting from competing cognitions may be an initial indicator of attitude change. If so, the information obtained from neural imaging techniques focused on activation in these brain regions may be useful in a variety of contexts, from initial message design to development of strategies to maintain healthy behaviors. For example, to the extent that the aversive state of cognitive dissonance is one key pathway to attitude change, health communication researchers may focus their efforts on refining the balance of this response and other factors within messages to maximally stimulate attitude change.

Indirect Effects

The research on dissonance described above, and the research that forms the basis for the IR model each contribute to our broader understanding of attitudinal processes, however, they do not speak directly to the core focus of this chapter (health-relevant media effects and the brain). Research on the power of messages to prime and influence individuals at the implicit level brings us a step closer. In examining non-deliberative media effects, Dal Cin and colleagues found that the more audience members identify with a smoking (vs. nonsmoking) version of the protagonist in a popular film, the stronger implicit associations between smoking and the self become (Dal Cin et al. 2007). This effect held true for both smokers and non-smokers, and extended to an increase in smokers' intentions to smoke (Dal Cin et al. 2007). These findings indicate that indirect health messages about smoking contained within mass media can relate to changes in individuals' self concept concerning smoking (Dal Cin et al. 2007).

Effects of mass media on implicit attitudes may also be a function of the media's role in shaping normative views. We engage in behaviors simply by being surrounded by the behavior of others (Bargh and Ferguson 2000). Watching someone else smoke at the bar can subconsciously entice a smoker to smoke more than usual (Conklin 2006). Additionally, getting caught up in the narrative of a character during a movie may have a similar effect (Dal Cin et al. 2007). Neuroscientists have found that when smokers watch scenes of smoking in a movie they show greater activity in the left anterior intraparietal sulcus and inferior frontal gyrus (IFG), regions associated with contralateral hand gestures (Wagner et al. 2011). One interpretation of these data is that environmental cues can serve as a trigger for habitual behaviors, such as smoking, in which we implicitly mirror the behaviors of others (Wagner et al.2011).

Persuasion

Although many effects studied by health communications researchers interested in mass media represent indirect media effects, there is a growing body of literature that examines neural processes underpinning persuasion and intended message effects. Neuroimaging research on persuasion has examined the differences in neurological activity associated with persuasive versus unpersuasive messages (Falk et al. 2009). Neural processes believed to be involved in mentalizing and perspective talking play a role in persuasive message processing (Falk et al. 2009). For example, activation of several key regions in the mentalizing system (Frith and Frith 2006), including the dorsal medial prefrontal cortex (DMPFC), posterior superior temporal sulcus (PSTS), temporal pole, and the left ventral lateral prefrontal cortex (VLPFC), are more active in response to messages that participants rate as persuasive, compared to those that they find unpersuasive (Falk et al. 2009).

However, understanding the differences in neurological activity between persuasive and unpersuasive messages is not the entire story. Differences in message presentation can alter this process. Messages can be specific to an individual by tailoring the message, or can be general, intended for mass viewing. Health communication studies in a number of domains show that tailored messages have a larger positive impact on behavior than untailored messages (Noar et al. 2007; Strecher 1999). Neuroimaging findings examining smoking cessation messages found that tailored messages involve brain regions associated with self-referential processing, specifically the rostral medial prefrontal cortex (MPFC), and precuneus/posterior cingulate (Chua et al. 2009). One possible interpretation of these findings is that self-referential processes are important to the success of smoking cessation messages (Chua et al. 2009). Authors suggest that self-referential processes allow smokers to personally evaluate their intentions and goals concerning quitting smoking (Chua et al. 2009).

Message source also contributes to the persuasion process (Petty and Cacioppo 1986). Effective persuasive messages have been tied to the expertise of the communicator (Petty and Cacioppo 1986). The effectiveness of expert source on persuasion depends on one's ability and motivation when processing a message (Petty and Cacioppo 1986); however, in general expert sources are more persuasive than non-expert sources (O'Keefe 2002; Petty and Wegener 1998). Neuroimaging studies have enhanced our understanding of messages delivered by an expert source compared to a source with low expertise (Klucharev et al. 2008). Expert influence was associated with increased left lateralized brain activity, medial temporal lobe, and caudate nucleus activity (Klucharev et al. 2008); these regions are believed to be involved in semantic elaboration, memory formation, and trusting behavior, respectively (Klucharev et al. 2008). Thus, these findings suggest that neural mechanisms associated with attention to expert sources may influence attitudes and memory in response to persuasive messages.

A study examining the "Message sensation value" (MSV) of public service announcements (PSAs) compared differences between PSAs with high versus low MSV, revealing that high MSV PSAs were associated with occipital cortex activity

while low MSV PSAs were associated with increased prefrontal and temporal activation (Langleben et al. 2009). Behavioral findings show that low MSV PSAs also lead to a higher rate of recognition, suggesting that low MSV PSAs lead to higher cognitive processing (Langleben et al. 2009).

Neuroimaging research has contributed to understanding persuasion by examining differences in neurological activity for persuasive versus unpersuasive, different heuristic cues, and diverse cognitive factors that influence the outcomes of persuasion. However, current neuroimaging studies have yet to systematically manipulate cognitive resource availability, and hence have been unable to speak to: (1) whether central versus peripheral processing is supported by a common neural mechanism engaged to varying degrees or if these routes represent the result of distinct neural networks, and (2) whether neuroimaging provides differing degrees of predictive insight about the process of attitude change under conditions of high versus low cognitive resources. Answering these questions will improve our ability to predict future attitudes in response to persuasive messages, will uncover knowledge about concordance between brain and self-report, and will enhance our knowledge of persuasion more broadly.

Social Influence/Conformity

Beyond effects of expertise, individuals are also highly influenced by the attitudes and norms expressed by others. Neuroscience research suggests that social norms affect neural responses differently depending on the value assigned to stimuli by peers. Research examining the social value of wine found that as the ostensible price of a sample of the same wine increased, activity in a region involved in encoding pleasant experiences (medial orbital frontal cortex (OFC), ventral medial prefrontal cortex(VMPFC) also increased, despite the wines actually being identical (Plassmann et al. 2008). Additionally, a study examining participants' preferences of symbols peers rated as popular, unpopular, or unrated found that the MPFC was activated more when viewing socially tagged versus unrated symbols (Mason et al. 2009). Findings suggest that the MPFC plays a role in tracking socially relevant information (Mason et al. 2009). Furthermore, using transcranial magnetic stimulation (TMS) to disrupt posterior medial frontal cortex processing has been shown to reduce conformity by reducing conflict monitoring associated by having differing opinions to a normative group (Klucharev et al. 2011).

Further supporting the role of the brain's reward system (Fig. 2) in promoting conformity, neuroimaging studies examining how the opinion of others affects our own valuations found that ventral striatum (VS) activity increases both when our preferences align with others and when receiving a reward (Campbell-Meiklejohn et al. 2010). Additionally, it is found that when viewing stimuli peers rate higher versus lower than participants there is increased activity in the VS and OFC, brain regions associated with reward (Zaki et al. 2011). It is thought that the VS responds to violations in expected rewards, whereas the VMPFC has been implicated in the

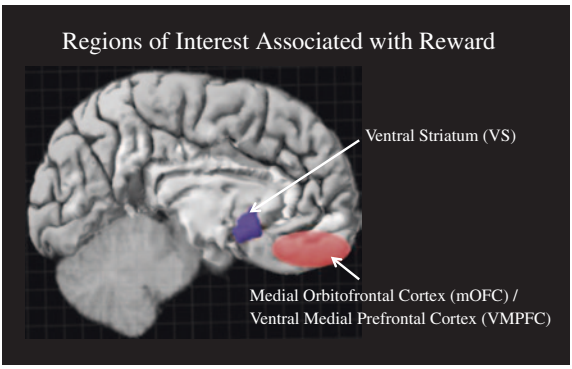

Fig. 2 Regions of interest associated with reward, consisting of the ventral striatum (VS) and medial orbitofrontal cortex (mOFC)/ ventral medial prefrontal cortex (VMPFC). Allen Brain Atlas Resources. Seattle (WA): Allen Institute for Brain Science. ©2009. Available from: http://www.brain-map.org

processing of the value of a reward (Berns et al. 2001; McClure et al. 2003; Schultz et al. 1997). Additionally, holding views that conflict with social norms has been found to (a) activate the rostral cingulate zone, a region involved in conflict or error monitoring of unfavorable outcomes (Klucharev et al. 2009), and (b) deactivate the VS, a key component of the brain's reward system (Klucharev et al. 2009).

Although persuasive messages can influence attitudes and behaviors, individuals have the ability to buffer their responses to persuasive message influences. When examining the effects of media influences on tobacco and alcohol use among adolescents, it is found that adolescents who score high on self-control measures are less influenced by media to use tobacco and alcohol than children who score low on self-control measures (Wills et al. 2010). Self-control reflects the ability to focus attention, delay gratification, and stick with a task until it is completed (Wills et al. 2010). Furthermore, brain regions associated with cognitive control, including VLPFC, DLPFC, MPFC, dACC, and precuneus may also aid in controlling affective responses, which may in turn reduce susceptibility to social influence (Lieberman 2010). Preliminary data examining the relationship between neural responses to exclusion and risky teen driving behavior in the presence of a peer suggests that increased activation of the social pain network (AI, subgenual ACC) in adolescents during social exclusion predicts risky driving behavior while in the presence of a peer in a separate session (Falk et al. Under Revision). However, response inhibition regions (right IFG, basal ganglia) appear to buffer social influence in some social contexts (Cascio In Prep).

Behavior Change

The neuroimaging studies reviewed above have demonstrated preliminary evidence for relationships between brain activity and social processes, including susceptibility to persuasion and social influence. Separate studies have examined the relationship between neural responses to health communication and the

behavior change that follows. For example, work in this area has used neural signals in MPFC to predict changes in sunscreen use one week following exposure to persuasive messages concerning sun exposure (Falk et al. 2010). Neural signals in MPFC predicted an additional 23 % of the variability in behavior above and beyond what self-report measures, such as intentions and attitudes, explained alone (Falk et al. 2010). In addition, a whole brain search for additional regions associated with behavior change revealed significant associations with the precuneus, PSTS, temporal parietal junction, and temporal pole, areas implicated in considering the mental states of others (Falk et al. 2010). These results suggest that incorporating neural data with self-report measures may provide additional information to develop predictive models. These findings also extend the use of neuroimaging to predict other types of behavior, as opposed to simply predicting immediate effects (Berkman and Falk 2013).

Extending the findings in the sunscreen study, Falk and colleagues examined smokers' neural responses to antismoking ad campaigns and subsequent smoking behavior (Falk et al. 2011). Consistent with the findings of the sunscreen study, research examining neural responses to antismoking advertisements found that MPFC explained 20 % of the variance in exhaled CO (a biological proxy for recent tobacco smoking) one month after initial fMRI and self-report measures (Falk et al. 2011). Thus, activation of the MPFC may serve as an indirect marker of future behavior change (Falk et al. 2011). Indeed, activity in the same region of MPFC that predicted individual behavior change during message exposure predicted population level behavior in response to health messages, and provided information that was not conveyed by participants' self-reports (Falk et al. 2012). These results extend previous findings to a more complex behavior than increasing sunscreen use and are also of practical importance, given that antismoking ad campaigns are a popular and common method for promoting smoking cessation (Popham et al. 1993; Vallone et al. 2011).

An important question in understanding the relationship between health communications and health behavior change is: What is the most effective way to deliver a health message? Technology has provided the field of health communication with a platform to reach larger audiences and to tailor the experience toward individual needs. This is in contrast to traditional mass media techniques that target a more general audience. At the same time, social neuroscience has provided techniques for researchers to explore the differences in how individuals neurologically process general versus tailored smoking-cessation messages. This is important in understanding what makes a tailored message more effective than a general persuasive message (Chua et al. 2011). Recall that tailored messages activate neural regions that are also activated in self-related processing, including regions of DMPFC identified in a localizer task (Chua et al. 2011). These studies have laid a foundation for understanding the links between health communications and associated behaviors, however, substantial work remains to be done to determine the precise psychological functions of brain regions involved.

Maintaining Behavior Change

Predicting the long-term success of quitting unhealthy habits is important to health professionals. Brain responses may be able to identify these characteristics. Social neuroscientists interested in the link between smoking cravings and smoking behavior have found that neural regions associated with response inhibition, right IFG, pre-supplementary motor area, and basal ganglia, were associated with decreased link between smoking cravings and smoking behavior—in other words, people who showed more activity in cognitive control regions during a basic response inhibition task also did not give into their cravings as easily during a real-world quit attempt (Berkman et al. 2011). Researchers examining smoking cessation found that neural activity in response to emotional and smoking related pictures predicted the long-term success of smoking cessation (Versace et al. 2011). Using ERPs it was found that smokers with lowered brain activity to pleasant stimuli had less success in abstaining from smoking in the long-term (Versace et al. 2011). Neuroimaging studies examining the mechanisms that support successful quitting provide health professionals with insights into intervention strategies that promote health behavior change and maintain a healthy lifestyle which may not be readily apparent with other methodologies (Grusser et al. 2004; Hester and Garavan 2004; Ray et al. 2008).

Future Directions

Neuroimaging augments our understanding of neurocognitive processes that respond to persuasive health messages. This understanding can help to predict future health behavior change. Findings from neuroimaging studies have explained variance above and beyond what traditional self-report explains, consistent with the idea that factors outside an individual's conscious awareness play an important role in understanding the effects of health communication. Studies have characterized a variety of individual and contextual factors that affect neural processing of persuasive messages and subsequent behavior. However, several open questions remain.

Currently, very little is known about the conditions in which brain, self-report, and indirect measures predict similar versus different outcomes. Additional exploration of the role of implicit versus explicit processing as well as affective versus cognitive processing will help to more accurately understand neural processes involved in persuasion.

Second, given the consistent finding across studies that MPFC and VMPFC are associated with conformity and behavior change, additional investigation of the psychological function(s) of these regions within the persuasion context is warranted. The MPFC has been implicated in multiple studies indicating it may be associated with implicit preferences (McClure et al. 2004), self-relevant future goals and perspective taking (D'Argembeau et al. 2010), and rating of current

stimuli in relation to an expected outcome (Knutson et al. 2001). Future work should isolate the implicated cognitive processes in order to further understand how the MPFC and VMPFC relate to persuasion and behavior change.

Third, health communications and health behavior change may affect individuals, groups, and populations differently with the influence of new media. For example, social neuroscientists examining new media, such as smartphones and social networking sites, may be interested in how neurocognitive processing of health communications are modified by technology. This is important as new media can change the way we are exposed to health communications, allowing for more efficient and effective communication.

Methodological Considerations

A complete review of neuroimaging methods and advances are beyond the scope of this chapter. Readers interested in different types of imaging methods, along with their strengths and weaknesses are referred to (Harmon-Jones and Beer 2009). However, across imaging modalities, several methodological considerations should be taken into account when planning future neuroimaging studies. One goal should be to increase sample size for studies that are concerned with between subjects differences (Lieberman and Cunningham 2009; Mumford and Nichols 2008). Having enough power is vital to detecting group differences, and many imaging studies are underpowered for this purpose (Desmond and Glover 2002).

Future studies can also benefit from the availability of new data analysis techniques. Building on past brain-mapping studies, *brain-as-predictor* approaches in which a priori ROI are targeted as predictors in statistical models (Berkman and Falk 2013) may improve our ability to predict behavior change and ultimately, to design and select optimally effective health messages. More sophisticated analysis techniques such as pattern classifiers can also be implemented. One such technique is multi-voxel pattern analysis (MVPA), which can examine differences in neural activation across brain regions as well as patterns within an ROI. MVPA may provide a sensitive method to detect neural network differences (Norman et al. 2006), which can be applied in a number of social and health-relevant domains. Detecting neural network differences allows researchers to differentiate different patterns within the same region, something that traditional univariate, general liner model-based fMRI analysis cannot achieve.

Finally, reverse inference problems make interpreting psychological processes from neuroimaging data difficult (Poldrack 2006). Reverse inference refers to the practice of inferring cognitive function based on activation of particular brain regions, which is different than measuring brain activity in response to cognitive tasks carried out in the scanner (Poldrack 2006). Using localizer scans–scans that define cognitive processes prior to the cognitive tasks of interest in order to pre-define regions of interest functionally can strengthen inferences (Lieberman 2010). TMS offers a way to disrupt neural processing during a neuroimaging task (e.g., during the time when certain persuasive messages are presented) (Hallett 2000), allowing researchers to examine if neural regions are necessary versus sufficient for cognitive processes of interest.

Conclusion

A growing body of research suggests that examining neural responses associated with processing health communications can aid in our understanding and prediction of attitude and behavior change. Pairing neuroimaging data with self-report, implicit, behavioral, and/or genetic measures ultimately will give scientists a more complete and potentially more efficient predictive model of behavior. Furthermore, neuroimaging can also inform psychological models of behavior change. In addition to health communications and health behavior change, this methodology may be of interest in the study of broader determinants of health including community violence, politics, education, and workplace dynamics.

Highlights

- Despite the success of prominent behavior change models in explaining the impact of health messages on behavior change, they are still limited. One difficulty in predicting health behavior change is the uncertainty in knowing who will successfully traverse the gap between attitudes, intentions, and behavior.
- Knowledge gained from neuroimaging may complement what we know from self-reports about how people process persuasive messages. In turn, gaining a firmer grasp on the underlying neural mechanisms involved can enable scientists to more accurately predict future behaviors.
- A growing body of research examining neural responses to health communications and other basic laboratory tasks has found that neural signals predict variability in behavior above and beyond what self-report measures explained alone.
- Neuroimaging is not a replacement for existing methodologies; we have the most to gain when multiple techniques are combined to understand behavior. This integration can be key in developing and strengthening theoretical knowledge and real-world applications.

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Chapter 5
Neurobiological Bases of Self-Reference and Deliberate Processing in Tailored Health Communication

Shaun Ho and Hannah Faye Chua

Introduction

Since the 1990s, health communication techniques and information technology have fueled the development of health communication programs that are customized ("tailored") for individual clients. To date, more and more tailored health communications can be delivered via Internet across multiple platforms on electronic mobile devices. The tailored health communication interventions have been developed in diverse settings, e.g., smoking cessation, weight management, exercise, etc. Research showed that *tailored* health interventions can be more effective in eliciting a positive health behavior change than *generic, one-size-fits-all* approaches (Brug et al. 1999; Lancaster and Stead 2005; Skinner et al. 1994; Strecher 1999). These exciting developments greatly help reach clients that are otherwise unreachable, reduce health problems that are preventable, and can help reduce the staggering health and societal costs. As a better understanding of psychological and neural mechanisms underlying the effectiveness of health communication may shape public health policy and research in the future, we aim to provide some useful information in this chapter.

Psychological Bases of Behavioral Changes

Here, we propose a theory of how behavioral interventions can change undesirable, unhealthy behaviors that may have perpetuated for some time. First, it is postulated that undesirable behaviors perpetuate, because they are represented in stable long-term memory (LTM) as schemas, which can be activated by environmental or internal cues, e.g., the sight of cigarettes or an urge in smokers. Since the schema,

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albeit undesirable, has persisted for some time, they become part of perpetual "self-concepts", which manifest as habitual patterns of thoughts, speech, feelings, volitions, and actions committed by the individual. Second, it is postulated that behavioral interventions in general, including health communication techniques, are professional attempts to tackle such perpetual self-concepts. Because these target self-concepts are stored as LTM we hereafter refer to it as target self-concepts or target LTM interchangeably. Third, a behavioral intervention is considered successful when it eventually transforms or eliminates the target self-concepts that give rise to the undesirable behaviors in question. Ideally, once the target self-concepts cease to exist, environmental or internal cues can no longer trigger the corresponding behaviors.

In health communication, technically, the processes of message tailoring involve (a) gathering data based on individual characteristics relevant to the intervention target (e.g., smoking cessation); (b) using algorithms to produce messages with strategies for personalization (designing the intervention message to a user), feedback (a review of what happened to the user), and content matching (affirming the motivation or needs and providing instructions matching the needs) (Hawkins et al. 2008); and (c) delivering the tailored messages to the client.

After the health messages are tailored and delivered, the outcome of tailored health communication interventions depends on whether the health messages can activate the target self-concepts through *self-reference processing* and whether the target self-concepts can be successfully transformed through *deliberate information processing*. The psychological and neural mechanisms of these two key processes are described below.

Self-Reference Processing

Self-reference is a central mechanism in message tailoring (Hawkins et al. 2008). In general, when the self is activated, it provides an integrative framework that promotes elaboration, organization of encoded information, and enhanced memory (Symons and Johnson 1997; Wheeler et al. 2007). Within an individual, multiple "encapsulated" self-related schemas (self-concepts) co-exist perpetually. In each moment, however, only some but not all self-concepts will be activated to influence the individual's thoughts, feelings, and behaviors. Shifting between one self-concept to another can take place rapidly, depending on inputs or primes (Wheeler et al. 2007). Primes that enhance assimilative change in the active self-concept can increase assimilative behavioral change, but primes that enhance contrast in the active self-concept can increase contrast in behaviors (Wheeler et al. 2007).

We postulate that the effects of the active self-concept primed by the tailored health communication depend on the assimilative (in-group) or contrast (out-group) relationship between a client and the perceived messages. If the client forms an in-group stance in the process, he or she will tend to assimilate the behavioral changes that are encouraged in the health communication. Conversely, if the client forms an out-group stance, he or she will tend to contrast the behaviors as instructed by the program. To illustrate, in the context of reading a testimonial, the self-reference processing may

operate in the following way: (a) Before or upon receiving a message, the client would form an in-group or out-group stance toward the intervention as a whole or a particular message, such as the success story depicted by another person; (b) the client's in-group/out-group stance becomes a basis on which his or her feelings and thoughts arise consciously or unconsciously, e.g., a client with an in-group stance would feel encouraged and/or rejoicing (e.g., Since we are similar, I am happy for this person and I would like to be just like him/her!); conversely, a client with an out-group stance would feel emotionally distant and/or jealous (e.g., Since we are different, I do not care why this person got better and I won't be as lucky as him/her!); (c) consequently, the client would be encouraged or discouraged to pursue the opportunity to change.

Thus, self-reference processing becomes *productive* if health messages prime active self-concepts that allow the client to form an in-group stance, and conversely anything that may prompt an out-group stance would be counter productive. Indeed, the in-group/out-group stance plays a pivotal role in various settings besides health communication. For examples, when the in-group stance toward others in general was augmented by practicing loving-kindness meditation, it promoted positive emotions and improved health outcomes (Fredrickson et al. 2008; Hofmann et al. 2011; Pace et al. 2009); conversely, when the out-group stance toward others was augmented by raising stereotypic identity threats toward college students of minority backgrounds (e.g., a female student in engineering), their learning performance was adversely influenced (Steele 1997).

Meanwhile, the role of emotions, like those arising on the basis of in-group/out-group stance, in health communication is debatable. One may argue positive emotions, such as warmth and joy, are helpful for health communication, as positive emotions can broaden one's awareness and encourage novel and exploratory thoughts and actions, which overtime would build skills and resources necessary for behavioral change (Fredrickson 2001). In contrast, positive moods can result in shallow, effort-minimizing information processing under certain circumstances (Forgas 1992).

While the functional significance of emotion in health communication is outside the scope of this chapter, strategically, to fully capitalize positive emotions resulting from productive self-reference processing without potential mental laxity as a side effect, it is important to engage the client's deliberate information processing, which is described next.

Deliberate Information Processing

In the context of health communication, deliberate processing refers to active and thoughtful information processing—considering things carefully in the context of a bigger picture, including one's own experiences (Kreuter and Holt 2001). Once the target self-concepts associated with the undesirable behaviors are engaged through the *productive* self-reference processing, as described above, deliberate processing is needed to transform the unhealthy patterns stored in the target self-concepts, i.e., the client should apply steady attention to the old target self-concepts and actively consider how they can be reprogrammed with the new information provided. Message

tailoring, therefore, should be designed to facilitate deliberate processing, by capturing the characteristics of the target self-concepts associated with the undesirable behaviors (e.g., asking about the triggers of smoking), providing feedback of such characteristics to the client to engage the target self-concepts with steady attention, and by providing solutions that can be integrated in the client's life to transform the target self concepts.

A common barrier that may interrupt steady attention to the target self-concepts is the emotion triggered by the health messages. As the message inputs successfully engage the target self-concepts related to stressors or risks that can trigger the undesirable behaviors (e.g., smoking), certain unpleasant emotional responses like craving or irritation, would arise initially. However, if the client can manage to maintain steady attention to the target self-concepts and remain unaffected by negative emotions, the emotional arousal should be habituated overtime. As evidenced in the literature, such initial emotional arousal and its habituation overtime are the hallmarks of positive outcomes of psychological interventions (Pascual-Leone and Greenberg 2007). Indeed, cognitive-based training that cultivates the non-judgmental concentration and deliberate transformation of negative emotions can promote healthy responses to psychosocial stresses (Pace et al. 2009).

Neurobiological Bases of Behavioral Changes

The advances in neuroscience have provided much background knowledge related to the mechanisms of behavioral change. Here, we will describe first the fundamental principles of the retention and modification of LTM that have been revealed at the cellular level. Second, we will describe at the system level the neural mechanisms associated with self-reference processing and deliberate processing, based on our own functional neuroimaging studies in smokers who underwent a web-based tailored message smoking cessation program.

Principles of Long-Term Memory Formation and Modification

The literature in basic cellular mechanisms of LTM formation and modification (Quirk et al. 2010) provides important knowledge about how the target LTM can be modified. Assuming the self-concepts in humans are stored in various forms of LTM, these cellular mechanisms can serve as principles for behavioral change. First and foremost, attention plays a critical role in encoding and retrieving LTM. According to the Synaptic Tagging and Capture Hypothesis (Redondo and Morris 2011), attention deployed to an event allows long-term potentiation (a form of memory at the neuronal level) to be formed by first "tagging" a synapse in a neuron and then supplying memory-sustaining proteins that are synthesized in the cell body to the tagged synapse. When the LTM is subsequently retrieved, attention is again needed to access

the synapses involved in the long-term potentiation. Furthermore, minutes after the LTM retrieval, the memory becomes malleable such that it can be abolished if certain memory-sustaining proteins were prevented from being synthesized in the neurons that store the LTM (Nader et al. 2000). Note that the memory-sustaining proteins act on specific synapses to maintain LTM (Martin et al. 2000; Si et al. 2010), other synapses in the same neuron do not necessarily capture these proteins.

These synaptic mechanisms provide bases on which the self-reference processing and deliberate processing during intervention can modify the target self-concepts (target LTM): First, attention to the (tailored) messages should retrieve the target LTM stored in the target population of neurons. Second, attention is paid to the instructions provided by the intervention in order to tag a synapse in the same neuron. Third, once a new synapse associated with the instruction is tagged, it can capture the memory-sustaining proteins that otherwise will be used solely for maintaining the old target LTM *in the same neurons*. As a result, the old memory is weakened and the new memory strengthened and the eventual therapeutic transformation accomplished by such processes combining sustained attention and cognitive reprogramming.

Neural Mechanisms of Self-Reference Processing

Individual-tailored cessation messages make specific references to the smoker's life, and therefore such tailored messages are expected to be rated as more self-relevant Strecher 1999). Message relevance has been known to subserve the enhanced effectiveness of the tailored messaging programs, as compared to generic interventions (Dijkstra 2005; Strecher 1999). Previously, we examined how smokers process tailored messages in two separate studies, involving separate groups of participants, to identify system-level neural mechanisms involved in behavior change (Chua et al. 2011, 2009). In both studies, midline brain regions shown by others to be involved in self-related processing, medial prefrontal cortex and precuneus, (Fossati et al. 2003; Kelley et al. 2002; Northoff et al. 2006; Ochsner et al. 2005; Phan et al. 2004), are indeed activated more by high-tailored messages, compared to low-tailored or generic messages. Notably, the tailored-messages-dependent neural responses in these two regions predicted the treatment outcome after 4 months (Chua et al. 2011), which attests to the crucial role of self-reference processing in the effectiveness of tailored health communication.

Neural Mechanisms of Deliberate Processing

As deliberate thinking is complex and covert, we explored to index the capacity of deliberate processing by measuring eye movement while the clients read the health messages and used this index to examine underlying neural mechanisms with neuroimaging data. In general, an eye-fixation during reading (~200–300 ms per fixation)

indicates attention to the reading material and is more likely to be located on content words ("walk, dog") rather than non-content words ("the, is") (Deans et al. 2010). The number of eye-fixation counts can be increased by shorter reading span (e.g., word-by-word reading), need to re-read (e.g., re-fixate after backward saccade), and deficiency in sustained attention (e.g., distraction). Indeed, the number of eye-fixation counts is known to be *inversely* related to reading fluency and comprehension. The literature shows that the eye-fixation count increases in patients with reading disability and attention-deficit hyperactivity disorder, as compared to healthy controls (Deans et al. 2010; Jones et al. 2008). Therefore, we postulated that higher eye-fixation counts would reflect less deliberate processing capacity as a result of fragmented reading, comprehension difficulty, or insufficient attention.

In the study to be described below, we measured eye-fixation counts with eye-tracking techniques to index individual differences in the capacity of deliberate processing. Participants read health messages provided in a smoking cessation program. We also explored the neurocircuitry associated with the deliberate processing capacity index in a functional MRI task. We hypothesized that the higher the capacity of deliberate information processing should predict better behavioral outcomes. Ninety-one smokers from the community who were interested to quit smoking participated in this study. Their average age was 37.5 years. They smoked an average of 16.7 cigarettes per day for an average of nearly 20 years. The participants completed a task involving tailored smoking cessation messages in an MRI scanner. During the task, the participants were presented with tailored instructional messages for smoking cessation and neutral messages unrelated to smoking. The instructional messages examined and addressed a smoker's barriers to quitting smoking (e.g., stress, weight gain, being in an environment of smokers). They informed smokers about steps for quitting and remaining abstinent in specific situations (e.g., "When you feel like smoking in the car, open the window and take some deep breaths"). On another day, participants also completed a standard web-based tailored smoking cessation program called Project Quit (Strecher et al. 2008) and started to quit smoking. The Project Quit program involved six sections and a total of 16 screens. Participants' eye movements were tracked with Tobii 120 eye-tracker system (Tobii, Sweden) as they were going over the web-based intervention. Real-life smoking cessation outcome was assessed 4 months following the tailored smoking cessation program in the 87 participants available for the assessment. More methodological details can be found in Chua et al. (2011).

Eye-fixation counts were measured when the participants were reading (1) tailored smoking-cessation instructions and (2) generic task instruction unrelated to smoking cessation (used as control for baseline deliberate processing). As mentioned before, higher eye-fixation counts should reflect less deliberate processing capacity, so we defined the *deliberate processing capacity index* as the inverse of the eye-fixation counts in the tailored smoking cessation instruction condition. In the results, we found that the deliberate processing capacity index predicted the quitting outcome, with those having higher *deliberate processing capacity index* more likely to quit ($\beta = -0.004$, *S.E.* $= 0.0013$, Wald $\chi^2 = 7.877$, $p = 0.005$), after controlling for the effects of age, gender, pack years, and fixation count in general task instruction. When we used the *deliberate processing capacity index* as

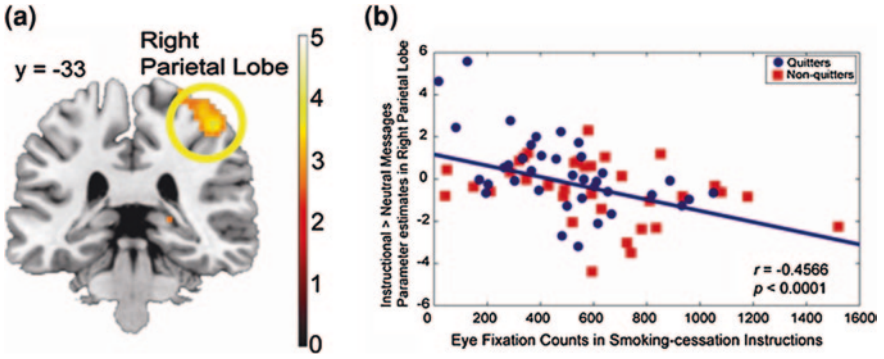

Fig. 5.1 **a** The deliberate processing capacity index, as defined as the inverse of eye fixation counts during the offline reading of tailored instructional messages in the web-based intervention program, was associated with greater differential activation in the *right* parietal lobe during the Instructional versus neutral messages conditions in the fMRI task. **b** The averaged parameter estimates of the Instruction—Neutral contrast in the *right* parietal lobe were inversely correlated with the eye fixation counts ($r = -0.4566$, $p < 0.0001$), which means the differential activation in this region was positively correlated with the deliberate processing capacity

a regressor with the brain activation patterns for instructional messages relative to neutral messages as the outcome variable, the activation in the right parietal lobe was found to be associated with increased *deliberate processing capacity index* (MNI coordinate: x, y, z = 45, −33, 57; 42 voxels, Z = 3.58, $p < 0.001$, see the figure). Indeed, increased activation in the right parietal lobe during instructional messages than neutral messages predicted better quitting outcome ($\beta = 0.389$, *S.E.* = 0.1537, Wald $\chi^2 = 6.408$, $p = .011$).

Taken together, the increased deliberate processing capacity was associated with increased neural activation patterns in the right parietal lobe, and both of them predicted smoking-cessation outcomes four months later. The right parietal lobe could be associated with sustained attention in smokers (Vossel et al. 2011). These results support the notion that the right parietal lobe may mediate deliberate processing by applying steady attention and potentially reading comprehension to the smoking-cessation instructions Fig. 5.1.

Summary

In an era with unlimited potential to apply information technology in every domain of life, science can be greatly advanced and enriched when information technology is applied within an appropriate framework. In this chapter, we provided a theoretical framework of behavioral change and described how the technologies of web-based message tailoring and eye movement measurement used in a smoking cessation program have assisted the researchers to efficiently study the underlying neural mechanisms. Since behavioral change is highly personalized, better understanding of underlying behavioral and neurobiological mechanisms

should help clinical and public health specialists to develop personalized interventions that are more effective than generic ones.

In terms of behavioral mechanisms, we postulated that the *activation* and *transformation* of the *target self-concepts* associated with target behavioral repertoires are the core components of behavioral interventions to cease undesirable, unhealthy behaviors. We highlighted two behavioral processes, *self-reference processing* and *deliberate processing*, to activate and transform the target self-concepts, respectively. The self-reference processing is especially productive if the clients hold an in-group stance to assimilate the health messages when the target self-concepts are activated. The deliberate processing encompasses steady attention and active thinking that are necessary to transform the activated target self-concepts.

In terms of understanding the neurobiological mechanisms of health communication and behavior change, we introduced cellular mechanisms of the LTM modification as the cellular principles of behavioral change. Using functional magnetic resonance imaging and eye tracking techniques, we found neural bases underlying the self-reference processing and deliberate processing that can predict the outcomes of the tailored smoking cessation program. The self-reference processing related neural responses in the medial prefrontal cortex and precuneus and the deliberate processing related neural responses in the right parietal lobe predicted the tailored message intervention outcomes four months later.

For public health scientists and practitioners, the quest for practical applications of this knowledge of behavioral change has just begun. How can we increase self-reference processing and how can we increase deliberate processing? There are many programs that already increase self-reference processing through providing tailored interventions using web-based technology. These can be extended to smart phone and tablet applications, or even old-time emails. To increase deliberate processing, public health professionals can think about making sure that the program can be read and understood by most people with lower reading levels. They can also target increasing sustained attention and defying negative emotional interferences by adopting techniques such as cognitive-based mindfulness training to intervention programs that they deploy.

Highlights

- This chapter describes two mechanisms involved in the efficacy of tailored health communications: self-reference and deliberate processing.
- Self-reference involves activating self-concepts that can promote change and is related to midline brain structures
- Deliberate processing involves sustaining attention and thinking and is related to the parietal lobe
- These two mechanisms should be the targets of interventions, with integrated information technology and mindfulness/contemplation training, to promote public health

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Part III
Health Behaviours

Chapter 6
Neurocognition and Medication Adherence in HIV-Infected Adults

Stella E. Panos, Sapna M. Patel, April D. Thames and Charles H. Hinkin

Introduction

Pharmacological advances in the treatment of HIV infection—referred to by the lay media as having a "Lazarus effect" due to its success—have transformed what was once a terminal illness into a chronic illness. As a result, individuals with HIV are living longer. But there is a catch. As succinctly captured by the ex-Surgeon General C. Everett Koop, even the most effective advance in pharmacotherapy is of little use if patients fail to adequately adhere to their medication regimen ("Drugs don't work if people don't take them"). Nearly 50 % of all adults in the United States are living with at least one chronic illness (Centers for Disease Control 2009) and 50 % of those individuals are poorly adherent to their prescribed medications (Sabaté 2003). The costs of non-adherence are staggering from both personal and public health perspectives. For example, an estimated 86,000 premature deaths can be prevented annually if patients were adherent to their prescribed antihypertensive medications (Cutler et al. 2007). Anywhere between one-third and two-thirds of medication-related emergency visit hospitalizations are related to failures in medication adherence, a cost that is estimated to approximate $100 billion annually (McDonnell and Jacobs 2002; Osterberg and Blaschke 2005).

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There exists an extensive body of research across diseases, as well as specific to HIV, that has examined predictors of medication adherence as well as interventions designed to improve adherence. With regard to HIV, medication adherence is associated with a wide range of factors, including: (a) those related to the patient (e.g., demographic factors, psychiatric illness, beliefs about medications and illness); (b) the medications prescribed (e.g., adverse side effects and complex dosing regimens); (c) the illness under treatment (e.g., HIV-associated cognitive dysfunction); and (d) the psychosocial environment (e.g., poor access to care, social support, and the patient-provider relationship) (Ickovics and Meisler 1997). This chapter will primarily focus on the relationship between cognition and medication adherence among HIV-infected adults, with a particular emphasis on older HIV+ adults, one of the fast growing subgroups in the HIV populace.

There are several shared factors that converge to make the study of neurocognition and medication adherence among individuals living with HIV, especially older individuals living with HIV, of considerable interest from a public health perspective. First, older adults are at particular risk for poor medication adherence secondary to cognitive compromise. The normal aging process and HIV infection are associated with decline in an overlapping array of neurocognitive abilities, including executive functions, working memory, attention, learning/memory, and speed of cognitive processing (Heaton et al. 1995; Hinkin et al. 1990, 2002b; Wendelken and Valcour 2012; Wilkie et al. 2000). By the year 2015, an estimated 50 % of the HIV-infected population will be over the age of 50 (Centers for Disease Control 2007) and these 'older' HIV+ individuals are three times more likely to develop HIV-associated dementia than younger HIV+ individuals (Valcour et al. 2004).

Second, both older adults and individuals living with HIV are more likely to require self-management of multiple medications for various chronic illnesses. Older individuals in the general population use up to 40 % of all prescribed medications (Vik et al. 2006), though they constitute only approximately 15 % of the population. Antiretroviral therapy for the treatment of HIV typically consists of a combination of at least three different classes of antiretroviral agents. This has traditionally required at minimum three different medications (often more) to be taken multiple times a day, though single pill combinations (typically a combination of two or more medications in one pill) are becoming more prevalent. In addition, it has been demonstrated that 89 % of older HIV+ individuals (age 55 years and older) have at least one comorbid condition (Shah et al. 2002). These individuals are more likely to take medications for a variety of comorbid chronic diseases, such as heart disease, diabetes, hypertension, and hyperlipidemia, to name a few.

Third, relative to other medication regimens, antiretroviral therapy requires meticulous adherence (90–95 % adherence levels) as suboptimal adherence can result in the emergence of treatment resistant viral mutations (Paterson et al. 2000). This dwarfs the level of adherence required for most chronic diseases (e.g., hypertension),

and underscores why this issue is of such public health concern. Unfortunately, only up to 50–60 % of HIV+ adults taking antiretroviral therapy maintain these optimal adherence levels (Gifford et al. 2000; Hinkin et al. 2004; Nieuwkerk et al. 2001), leading to what can be a rather precipitous decline in immunocompetence and the advent of untoward clinical consequences.

Finally, due to recent developments, the number of HIV+ individuals prescribed antiretroviral therapy will likely increase. Historically, many HIV+ adults have refused to initiate pharmacotherapy, holding off until absolutely necessary. However, it has just recently been recognized that early initiation of antiretroviral therapy reduces risk of transmission to uninfected sexual partners by 96 % (HIV Prevention Trials Network 2011). Moreover, even HIV- individuals who are at heightened risk for contracting HIV (e.g., those in a HIV sero-discordant relationship) are being placed on antiretroviral therapy given recent approval of Truvada for prophylactic use (US Food and Drug Administration 2012). Given the potential that suboptimal adherence can lead to the development of treatment resistant viral strains, rigorous adherence to antiretroviral therapy is therefore an increasing public health concern.

This chapter is intended to provide a broad overview of factors associated with medication adherence to antiretroviral therapy, with particular emphasis on the most current knowledge regarding the relationship between neuropsychological functioning and medication adherence. We will begin with a brief review of some of the many methodological complexities important to consider in the study of medication adherence and cognition. The balance of the chapter will focus on key neurocognitive, psychiatric (including substance use), and psychosocial factors that have been shown to be related to medication adherence in the HIV-infected population.

Methodology

Medication Adherence Measurement Techniques

Medication adherence involves taking the correct dosage of a medication (e.g., the correct number of pills), at the correct time, while adhering to specific instructions (e.g., with or without food; Gould et al. 1999). A number of methods have been developed to measure medication adherence, each with inherent advantages and disadvantages in terms of measurement accuracy and feasibility. These methodologies fall into two broad categories, subjective (e.g., self-report) and objective (e.g., pill counts, electronic monitoring devices) techniques (see Table 6.1; Castellon et al. 2009). Although a comprehensive review of each of these techniques is beyond the scope of this chapter, we will briefly review several commonly used approaches.

Self-report is the most widely used method to track adherence in both research and clinical settings because of its low cost and ease of administration. Patients are asked to recall how adherent they were (often using a Likert Scale) to their prescribed medication regimen over the course of a specified time period. While the

Table 6.1 Adherence Methodologies

Measures	Description
Subjective measures	*Description*
Self-report	The patient is asked to recall if they took their medications as directed typically using a Likert Scale
	Strengths Cost-effective, ease of data collection
	Weaknesses Patients may not be able to accurately recall; may over-estimate adherence
Clinician ratings	The physician assesses and rates how well the patient has adhered to their medication regimen via questioning in terms of their functional status, attitudes toward taking medications, medication side effects, and level of participation in their medication treatment
	Strengths Easily obtainable
	Weaknesses Patients portray their attitudes toward medications as being more favorable than they actually are; overestimation of adherence rates by the clinician
Objective measures	*Description*
Pill counts	The physician calculates the number of pills that should remain at their next visit, based on the number of pills prescribed and how many they should have ingested
	Strengths Straightforward, easy to calculate
	Weaknesses Assumes missing pills were consumed and not discarded/ misplaced; easy for patients to calculate and, therefore, manipulate their pill counts to appear more adherent (can be countered by "unannounced pill counts"); does not track whether patients are taking these medications at the right time
Pharmacy refill records	The physician examines the patient's refill records
	Strengths Cost-effective; can be easily obtained
	Weaknesses Pharmacy records have to be centralized; *assumes* that patients who are refilling their medications on time are adherent; cannot determine whether patients are taking their medications on time
Laboratory based analog measures	Tests that assess the patient's ability to self-administer and manage fictitious medications (e.g., sorting, organizing and planning for trips)
	Strengths Attempts to assess real world medication management abilities
	Weaknesses Tasks may not simulate the patient's medication behaviors outside of the laboratory; understudied area
Blood levels	The patient is administered a blood test in order to determine if they are adherent to their medications
	Strengths Objective marker of medication adherence; Precise quantification
	Weaknesses Only useful for medications taken recently and is not helpful for determining whether the patients are typically adherent

(continued)

Table 6.1 (continued)

Measures	Description
Medication event monitoring system (MEMS)	This utilizes pill bottle caps that record the date, time, and duration of bottle opening
	Strengths More accurate than pill counting and self-reporting (can also ensure that patients are taking their medications on time)
	Weaknesses Bulky nature of the bottle, which can result in the patient removing extra doses for later ingestion (i.e., "pocket-dosing"); pills cannot be organized; the data must be downloaded; may underestimate adherence rates
MedTracker	This utilizes a pillbox with multiple compartments and an electronic tracking device
	Strengths Continual tracking of adherence without downloading information, can organize pills by day of the week, and track adherence to multiple medications (which could potentially allow for real-time interventions)
	Weaknesses Not optimized for size, the number of compartments may not be ideal for users; may be difficult to distinguish adherence to different medications

Adapted from Castellon et al. (2009)

advantages to this approach are clear, there are considerable limitations; most notable is the consistent finding that self-report tends to overestimate actual adherence rates (Arnsten et al. 2001; Liu et al. 2001). When using self-report methodologies, shorter recall intervals (e.g., 4 days) have been found to be more closely related to objective measures (Levine et al. 2006). For obvious reasons, however, relying on self-report of cognitively impaired patients is problematic (Thames et al. 2011a).

As an alternative to subjective measures, the Medication Event Monitoring System (MEMS) (Aprex Corp, Union City, California) was created. In its most basic form, this is a pill bottle with a microchip-embedded cap that records the precise date, time, and duration of each bottle opening. When this is used, medication adherence is typically calculated as the total number of MEMS bottle openings divided by the total number of bottle openings that should have occurred over a specified time period. There are some logistical complexities

to this approach, including its cumbersome nature. This may cause patients to remove extra doses from their MEMS for later ingestion. This approach also prevents individuals from placing their medications into organized pillboxes that aid in medication taking behavior. Perhaps as a result of this, researchers have found that MEMS may underestimate medication adherence (Liu et al. 2001). It should also be noted that studies using MEMS often track one medication as opposed to multiple medications (for logistical reasons). Therefore, these more general associations may in fact also underestimate the effect of cognition on adherence rates to multiple medications. There is no gold standard in regards to measuring medication adherence. However, there is evidence to suggest that objective measures (including MEMS) are better approaches compared to self-report, though a multimeasure methodological approach is ideal (Arnsten et al. 2001; Liu et al. 2001). More recently, the MedTracker (Hayes et al. 2006) and the Med-eMonitor devices (www.informedix.com; Harberer et al. 2012) were developed to overcome some of the MEMS limitations.

Pill count is an objective and straightforward technique that has been used to measure adherence rates. Clinicians calculate the number of pills that should remain based on the number of pills initially possessed and the number of pills that should have been ingested. However, this is easy for patients to calculate and they may remove extra doses from their pill bottle prior to appointments in order to appear more adherent. To overcome this limitation, "unannounced pill counts" (Bangsberg et al. 2001) can be condutced. Unannoucned pill counts have been shown to correlate with HIV RNA and medication adherence electronic monitoring devices (Haberer et al. 2012). Unannounced telephonic pill counts is another twist to this technique.

Precise quantification of medication adherence can be ascertained through blood tests. However, one drawback of this technique is that it is not useful for examining adherence rates for medications that metabolize rapidly. Second, blood levels will only detect *recent* medication behaviors, but do not provide insight into the patient's *typical* medication taking behaviors.

Pharmacy refill records can also be used to assess medication adherence. It is assumed that if the patients are refilling their medications on time, it is likely that they are taking them as prescribed. Although this technique is cost-effective, it requires centralized pharmacy records and *assumes* that patients are taking their medications as prescribed.

Laboratory-based performance measures (analog measures) of medication management have been increasingly used by researchers, who are interested in finer-grained examination of adherence behavior. Medication management refers to select aspects of medication taking abilities, such as the ability to read and understand labels on pill bottles, and the ability to know when to refill their medications, how many pills are required for each dosage, and how to correctly place pills in a pillbox based on the instructions on the labels. Analog measures have been found to correlate with self-reported medication adherence (Albert et al. 1999). To our knowledge, their relationship to other measures of medication adherence has yet to be assessed.

Measurement of Cognition in the Study of Medication Adherence

A number of different techniques have also been used to measure cognition in medication adherence studies. There remains significant methodological variability within the literature assessing cognition and the impact of cognition on adherence to antiretroviral therapy (Lovejoy and Suhr 2009; Robertson et al. 2009). HIV predominantly affects fronto-subcortical regions of the brain, resulting in deficits in executive functions, learning and memory, processing speed, attention, and motor functioning. Researchers must decide whether they will measure a single cognitive domain (e.g., memory) or multiple domains. As we will discuss below, medication taking-behavior is a complex behavior enlisting multiple domains and measuring a single construct (e.g., memory) may not fully capture the manner by which cognition affects medication adherence. Neuropsychological test selection, the number of tests used to assess cognitive domains of choice, and methods used for post-processing neuropsychological test data (e.g., whether to employ demographically adjusted normative data; how to best collapse data for analysis) must also be considered. Since the advent of antiretroviral therapy, milder forms of HAND have become more prevalent and test selection aimed at accurately capturing milder forms of cognitive impairment is crucial. Furthermore, the demographic composition of the HIV-infected populace has changed considerably over time, with the result that researchers must now carefully consider how demographic factors may affect neuropsychological test performance over and above the effects of HIV infection itself. In a recent review of studies examining the impact of HIV-associated neurocognitive dysfunction (HAND) on adherence, Lovejoy and Suhr (2009) found that studies that used multiple measures of cognition were more likely to detect a relationship between cognition and medication adherence than were those that relied upon a single screening tool. They concluded that comprehensive neuropsychological batteries coupled with the use of demographically corrected normative data should be viewed as the ideal approach that should be employed whenever possible unless logistical constraints demand otherwise.

Neuropsychological Functioning and Medication Adherence

Cognitive Dysfunction and Medication Adherence

Although it was long recognized that impaired cognition can be an important barrier to treatment (Geller 1982; Parkin et al. 1976), formal study using objective measures of cognition and their relationship to medication adherence did not emerge in the general medical literature until about two decades ago (Farmer et al. 1990; Meyer and Schuna 1989) and in the HIV literature until about 10 years

ago (Avants et al. 2001; Hinkin et al. 2002a). Since then, a large body of research has accrued and converged on the clear conclusion that impaired cognition has an adverse impact on medication adherence. Difficulties with medication adherence have been linked to a wide range of neurocognitive dysfunction, including deficits in executive function, complex attention/working memory, learning and memory, psychomotor processing speed, and motor functioning (for review, see Lovejoy and Suhr 2009). The fact that deficits in a wide array of neurocognitive abilities can lead to compromised adherence is not surprising given that medication adherence is indeed a rather complex behavior that would arguably enlist multiple cognitive functions (e.g., comprehension of instructions and of risks of non-adherence, the ability to develop a systematic plan for pill taking that requires a significant degree of forethought and initiation, the ability to remember to take the medications at the right times in the face of concurrent demands in one's day-to-day life) as well as relatively more simple behaviors (e.g., the ability to open a pill bottle). Hinkin et al. (2002a) found that HIV+ adults who presented with global cognitive impairment (as assessed by a battery of neuropsychological tests) were more than twice as likely to be non-adherent than those with intact cognition. Among individual cognitive domains, higher order neurocognitive processes (i.e., executive functions, learning/memory, and complex attention) appear to be more robustly related to medication adherence (Hinkin et al. 2002a; Lovejoy and Suhr 2009).

Longitudinal Studies of Cognition and Medication Adherence

Although the majority of studies assessing the relationship between cognition and medication adherence to antiretroviral therapy have been cross-sectional/correlative in nature, second-generation studies of medication adherence and cognition have begun to focus on "cause and effect" questions. To the extent that medications beneficially impact cognition (as is the case with many medications, including antiretroviral therapy), the relationship between cognition and medication adherence should be conceptualized as bidirectional in nature. As such, we would expect not only that cognitive dysfunction should lead to poor adherence, but also that poor medication adherence should lead to worsening neuropsychological dysfunction. Disentangling the effects of each (cognition and medication adherence) requires sophisticated longitudinal studies that assess both medication adherence and neurocognition at multiple time points. Two longitudinal studies from our laboratory have directly tackled this chicken and egg conundrum. Employing path-analysis in a sample of 91 HIV+ adults, Ettenhofer et al. (2010) measured medication adherence prospectively over the course of 6 months using MEMS caps and assessed cognition at baseline and 6 months later. As seen in Fig. 6.1, baseline cognition was predictive of medication adherence over the course of the 6 month study. Analyses by discrete cognitive sub-domains revealed that this was driven primarily by executive functions and learning/memory. After controlling for the inherent correlation between cognition assessed at both time

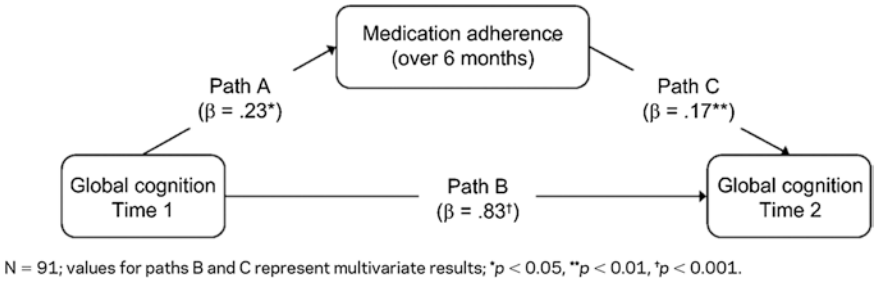

Fig. 6.1 Model of longitudinal path analysis of global cognition and medication adherence. Reproduced with permission from Wolters Kluwer Health. *From* Ettenhofer et al. (2010, p. 1219)

points (before and end of study), they found that higher levels of medication adherence across the 6 months were predictive of better cognition at the end of the study. Analysis by discrete cognitive domains revealed this was primarily driven by executive functions, complex attention, information processing, and motor functioning.

Using a different longitudinal methodology, Becker et al. (2011) compared the medication adherence trajectories of HIV+ patients who exhibited cognitive decline and those who did not over the course of 6 months. Those who exhibited cognitive decline over the course of the 6 months also evidenced steeper adherence declines over time. In the final month of the study, those with cognitive decline evidenced 52 % adherence levels compared to the 66 % adherence levels of the cognitively stable group. Follow-up analyses revealed that learning and memory in particular was associated with changes in adherence.

Taken together, these studies suggest that a variety of cognitive functions are related to medication adherence. The relationship between cognition and medication adherence is bidirectional, with higher order cognitive functions (executive functions and learning/memory) appearing to be more robust predictors of medication adherence. Declines in cognition over time result in corresponding declines in medication adherence. Conversely, medication adherence is predictive of a wider range of neurocognitive changes. Executive functioning in particular appears to be involved both directions of the relationship between cognition and medication adherence and is therefore a prime target for focused intervention.

Interactions Between Cognition and Other Variables

Age

In general, Dr. Koop would be most pleased with older HIV+ adults, as they have been shown to be far more adherent than are younger patients. Assessing

medication adherence over the course of a month, Hinkin et al. (2004) found that older HIV+ individuals (individuals 50 years of age and older[1]) demonstrated significantly better adherence rates (87.5 %) to antiretroviral therapy compared to younger HIV+ individuals (78.3 %). Using adherence cutoff scores to classify patients as "good adherers" (95 % adherence or better) and "poor adherers" (less than 95 % adherence levels), they found that older individuals were three times more likely to be classified as good adherers. This beneficial "effect" of older age on medication adherence has been consistently replicated (Becker et al. 2002; Halkitis et al. 2008). A variety of explanations have been advanced, including the possibility that older individuals are more accustomed to taking medications for other age-related illnesses, are less burdened by lifestyle alterations necessary for successful adherence, and have an increased appreciation of their own mortality and therefore increased motivation to be medically compliant.

However, while medication adherence levels are typically higher among older adults, older adults appear to be more susceptible to the deleterious impact of cognitive dysfunction on medication adherence. Finer-grained analyses conducted as part of the abovementioned study performed by our group found that an overwhelming majority of *older* patients who were classified as "poor adherers" were cognitively compromised. In contrast, only 35 % of those classified as "good adherers" were found to demonstrate cognitive dysfunction (Hinkin et al. 2004). In a follow-up study, we assessed the relationship between age and cognition on medication adherence more directly (Ettenhofer et al. 2009). Using a large sample ($N = 431$) and sophisticated statistical analyses (structural equation modeling), we found that neurocognitive impairment was associated with poorer medication adherence among older individuals, but not among their younger counterparts (see Fig. 6.2).

As mentioned previously, researchers are increasingly employing laboratory-based analog tasks to examine aspects of medication taking abilities. One such measure, the medication management task (MMT; Albert et al. 1999), has been refined by Heaton et al. (2004) in their work with HIV-infected patients. Our group employed the MMT to further assess the relationship between cognition, age, and medication management and found that medication management abilities correlated with a wide range of cognitive abilities, including executive functioning, attention/working memory, verbal fluency, and spatial processing (Thames et al. 2011b). As seen in Fig. 6.3, cognitively impaired individuals, particularly older patients, performed significantly worse on the medication management task than did younger patients. These findings suggest that cognition can impact medication adherence via some of the more basic aspects of medication management as well as some of the more complex aspects (e.g., planning ahead, remembering to take

[1] Readers familiar with gerontology research, or who themselves are on the far side of 50, might balk at the use of age 50 to define "older" adults. This cut point was not arrived at arbitrarily but instead has its roots in the proceedings of several working groups convened by the NIH in the late 1990s/early 2000s on this topic when the "graying" of the HIV epidemic was first recognized. Now that increasing numbers of HIV+ adults are living into their 70s and beyond, it may be time to soon revisit and revise this convention.

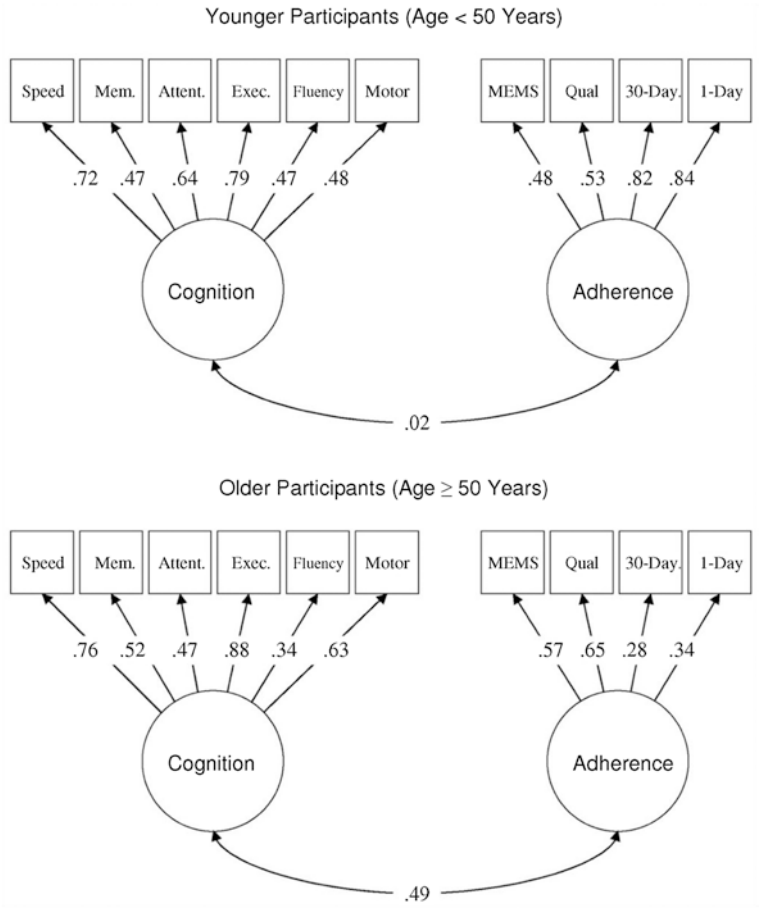

Fig. 6.2 Latent model of cognition and medication adherence among younger and older HIV+ adults. Reproduced with permission from American Psychiatric Publishing, Inc. *From* Ettenhofer et al. (2009, p. 287). *Notes* Mem.: memory; Attent.: attention; Exec.: executive; Qual.: qualitative self-report; 30 day: 30 day self-report; 1 day: 1 day self-report.Standardized values shown from model C_0. Factor loadings of 1 day self-report have been reversed for ease of interpretation

the medications at the right times in the face of concurrent demands in one's day-to-day life). This suggests that the MMT has potential for providing clinicians with a tool for identifying patients who need support with some of the more concrete aspects of medication management.

Regimen Complexity

Regimen complexity (e.g., dosing frequency, number of medications) has long been recognized as a factor to adversely impact medication adherence across a variety of

illnesses, including HIV (for reviews, see Ammassari et al. 2002; Claxton et al. 2001; Ingersoll and Cohen 2008; Iskedjian et al. 2002). As the number of medications and/or dosing frequency increases, medication adherence tends to decline. From a neurocognitive standpoint, select populations may be at particular risk for poor medication adherence secondary to regimen complexity. Assessing the effects of regimen complexity (once or twice daily vs. three or more times daily) and cognition on MEMS cap adherence in an HIV+ sample, Hinkin et al. (2002a) found main effects for cognition and regimen complexity as well as an interaction between cognition and regimen complexity. Individuals who were cognitively compromised and who were prescribed a more complex dosing regimens evidenced the lowest adherence rates (see Fig. 6.4). Complex dosing regimens did not pose disproportionate difficulty for cognitively

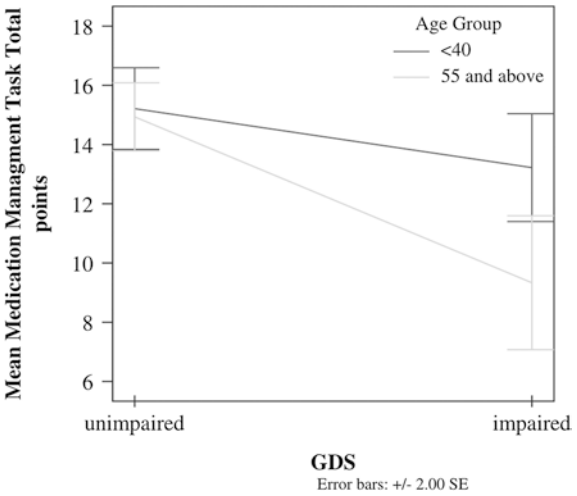

Fig. 6.3 Age and group differences on medication management task (mean scores represented for ease of interpretation). *GDS* Global deficit score. Reproduced with permission from Taylor and Francis, Ltd. *From* Thames et al. (2011b, p. 204)

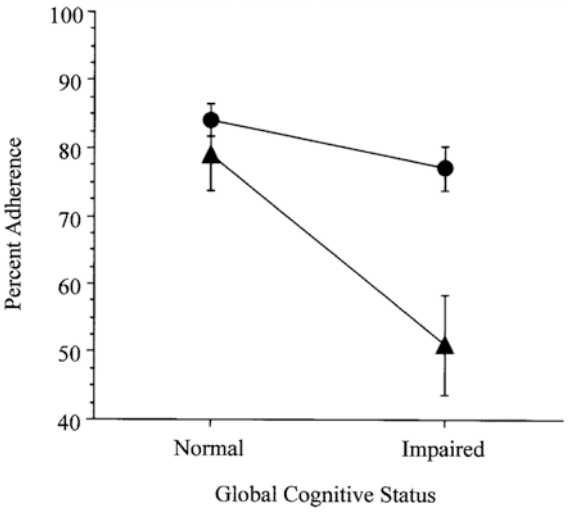

Fig. 6.4 Relationship between cognitive status, regimen complexity, and medication Adherence among HIV-infected adults. Reproduced with permission from Wolters Kluwer Health. *From* Hinkin et al. (2002a, p. 1947)

intact adults. Analyses by discrete neurocognitive domains revealed that this interaction was primarily driven by higher order cognitive processes (executive functions and higher order attentional processes), but not memory. These findings suggest that medication-specific factors such as complex dosing regimens can play an important role, particularly if individuals are experiencing significant executive dysfunction.

Relationship Between Broader Aspects of Cognition and Medication Adherence

Prospective Memory

Prospective memory (i.e., "remembering to remember") also appears to play a critical role in medication adherence. This refers to one's ability to execute a future intention (e.g., remembering to take one's medication at lunchtime) and is dependent on a variety of cognitive processes (as opposed to discrete areas of neurocognitive functioning that have been traditionally assessed in neurocognitive studies of medication adherence). In order to execute a future intention, individuals must be able to pair their intention with a retrieval cue (i.e., a specific time or event) and be able to maintain this intention-cue pairing—via automatic and strategic monitoring- while they are engaged in other tasks. They must subsequently be able to detect the cue and then follow through with the intention (McDaniel and Einstein 2007; Woods et al. 2008). The process of "remembering to remember" is dependent on the prefrontal cortex (Simons et al. 2006). Woods et al. found prospective memory to be a powerful predictor of self-reported medication adherence (2008) and objective measures of medication adherence (2009) in HIV that independently accounted for predictive variance over and beyond other cognitive, psychiatric, psychosocial, and environmental predictors of adherence. As discussed by these researchers, poor medication adherence may result from an inability to strategically allocate cognitive resources.

Health Literacy

Low health literacy has also emerged as a critical factor associated with a variety of adverse health outcomes, including medication-taking behavior. Broadly defined, health literacy includes the ability to understand instructions on prescription drug bottles, appointment slips, medical education brochures, doctor's directions and consent forms, and the ability to negotiate complex health care systems (US Department of Health and Human Services Office of Disease Prevention and Health Promotion 2010). While we have previously discussed how these skills rely heavily on intact cognitive functions, even basic literacy skills contribute to the successful management of medications (Kalichman et al. 1999; Waldrop-Valverde et al. 2010). Brief

interventions that increase HIV/AIDS and medication knowledge and self-efficacy have shown to be fruitful in increasing adherence in a sample of HIV+ individuals with low health literacy (Kalichman et al. 2005). This is an important finding, as the US immigrant population is rapidly growing with the number of individuals with limitations in health literacy increasing as well. The current challenge, both scientifically and clinically, is to continue to identify methods for delivering effective health communications to immigrants and other marginalized groups with low literacy skills to help recognize, minimize, and respond effectively to potential health problems.

Psychiatric/Psychological Functioning and Medication Adherence

Up until this point, we have focused on the effects of cognitive dysfunction on medication adherence. However, medication adherence is related to a far wider variety of factors. Two such factors that have a relationship with both cognition and medication adherence are psychiatric disturbance and substance use and abuse.

Psychiatric Functioning

In the HIV population, there is a high prevalence of psychiatric disorders, with approximately 50 % of individuals screening positive for one or more disorders, including depression and anxiety (Bing et al. 2001). These rates are considerably higher than rates found in the general population (Blazer et al. 1994). Bing et al. (2001) found that rates of depression were five times higher than the general population. The adverse effect of psychiatric disorders on medication adherence has been documented in a wide range of illnesses and has received considerable attention in HIV. Similar to the effects of cognition on medication adherence to antiretroviral therapy, individuals who are depressed are up to three times more likely to be non-adherent than non-depressed HIV+ individuals (Ammassari et al. 2004). There are a variety of possible mechanisms that may account for this. For example, symptoms associated with depression (e.g., sadness, lack of motivation, fatigue, and hopelessness) can often be debilitating for individuals, which can lead to self-neglect and poor adherence behaviors (e.g., not getting their prescriptions filled). Furthermore, depressed individuals may be more likely to drive away their social support through isolative behaviors, thereby not being able to rely on their support for assistance with medications.

A complicating element, however, is the fact that psychiatric disorders are often accompanied by a variety of cognitive difficulties. Determining the source of poor medication adherence, therefore, is critical for the selection of successful treatment interventions. Two psychiatric conditions that warrant particular attention in this

regard are apathy and irritability. These neuropsychiatric conditions have emerged as critical co-morbid conditions that are believed to be direct manifestations of underlying HIV-associated neuropathology rather than a psychological reaction to a life-threatening illness (Castellon et al. 1998; Cole et al. 2007). They have begun to receive increased attention as they relate to deficits in executive dysfunction, including working memory deficits, learning efficiency, and cognitive flexibility (Bungener et al. 1996; Castellon et al. 2000; Cole et al. 2007; Paul et al. 2005). Patients presenting with these psychiatric symptoms (compared to other psychiatric disturbances such as depression) may be at particular risk for experiencing difficulty adhering to medication regimen as a result of neurocognitive dysfunction. Formal study assessing the relationship between these symptoms and medication adherence has yet to be conducted, however. Preliminary work from our laboratory suggests that both apathy and irritability are predictive of longitudinal medication adherence even after controlling for the effects of depression and cognition (Panos et al. 2011). Given these emerging findings, further study is clearly warranted.

A critical factor that warrants attention for clinicians treating individuals with both HIV and psychiatric dysfunction is accuracy of self-report of medication adherence. Decisions made by clinicians about treatment efficacy largely rely on patient self-report. If patients report they are adhering to their regimen and continue to evidence precipitous decline in immunocompetence, this is taken as evidence that their current regimen is not effective and alterations in their regimen are made, perhaps unnecessarily. As we mentioned previously, there are only a limited number of antiretroviral medications available for use, limiting the number of possible regimen alterations available to the treating clinician. We have found that HIV+ individuals with psychiatric disturbance are not as accurate in identifying reasons for non-adherence (Thames et al. 2011a). In this study, depressed individuals were more likely to report that cognitive difficulties interfered with their abilities to take their medications. However, upon formal testing, they did not exhibit any difficulty managing their medications. Conversely, individuals who were cognitively impaired were more likely to be unaware of any difficulty managing their medications, and thus denied having any difficulty in this regard. However, upon formal testing, the cognitively compromised subjects evidenced considerable difficulty managing their medications. Taken together, this highlights the importance of considering depression and cognitive ability when assessing self-reported medication behaviors. Furthermore, these findings implicate the use of objective instrumental activities of daily living measures (versus the use of self-report) in order to accurately detect declines in medication behaviors, and subsequently guide treatment interventions.

Substance Use

In the HIV-infected population, rates of substance abuse/dependence are particularly high, with nearly 50 % reporting the use of illicit substances over the previous 12 months, and 12 % screening positive for current dependence

(Bing et al. 2001). Lifetime diagnoses of drug and alcohol abuse/dependence are yet higher (Dew et al. 1997; Rabkin 1996). The negative impact of substance use/abuse on medication adherence, especially stimulants, has received considerable attention (Fogarty et al. 2002; Hinkin et al. 2007; Howard et al. 2002; Meade et al. 2011). In a study from our laboratory assessing medication adherence prospectively over the course of 6 months, individuals with recent drug use were four times more likely to be non-adherent to antiretroviral therapy than were those who were drug-free (Hinkin et al. 2007). Subsequent analyses in this study found that stimulant use (cocaine and amphetamine) was particularly deleterious on medication adherence, with participants who tested positive for stimulants at least once over the course of the 6 month study being seven times more likely to be classified as "poor adherers." A number of mechanisms have been proposed to explain the manner by which drug use may impede medication adherence. These include stable psychological traits that characterize individuals using drugs, the interruption of daily routines during drug use that serve as cues for taking medications, and the effect of drug-induced cognitive dysfunction (Gorman et al. 2009).

As mentioned throughout this chapter, determining the specific basis for poor adherence in crucial for the development of successful treatment interventions. There has been a limited amount of work aimed at directly assessing which of the abovementioned factors may account for poor adherence among drug users in the HIV populace. Meade et al. (2011) compared adherence rates and neurocognitive performance between HIV+ individuals who met diagnostic criteria for current cocaine dependence and HIV+ individuals who were not dependent on any drugs. They found that individuals who were cocaine-dependent exhibited both lower medication adherence rates and poorer neurocognitive functioning. Subsequent analyses revealed that neurocognition partially mediated the relationship between stimulant use and medication adherence in this sample.

There is evidence to suggest that the relationship between substance use and medication adherence may also be mediated by other factors. In the abovementioned study from our laboratory, we compared medication adherence rates for individuals who had recently used stimulants (within 3 days of testing) with their adherence rates when they had not used drugs within the past 3 days (as indexed by urine toxicology assays). Despite the fact that all of these subjects had used stimulants at some point during the 6 month study, we found that during periods of even brief abstinence their adherence rates returned to normal (Hinkin et al. 2007). This lends support for the contention that drug use may adversely impact adherence by altering routines that serve as cues for taking medications. This also suggests that the adverse effects of drug use on adherence should be conceptualized as a transient and reversible "state" rather than some immutable "trait" that defines drug users (Malta et al. 2008, 2010). For individuals who use drugs, therefore, interventions aimed at improving adherence during times of drug use may be warranted.

Psychosocial Factors

We would be remiss not to discuss at least briefly some of psychosocial theories that have been set forth to describe medication taking behavior. It is within this broader psychosocial context that the aforementioned factors interact. In general, psychosocial theories focus on larger internal (e.g., beliefs about illness and treatment) and external (e.g., social support, access to resources) factors that affect health behavior. Several theories have been developed over the course of the last several decades to explain health behavior. In the context of medication adherence, for example, the Health Belief Model (HBM) (Rosenstock 1974) posits that adherence is optimal when individuals perceive that they are susceptible to illness (e.g., the belief that they will get sick should they not take their medications), perceive that the consequences of this illness can be severe, believe that the prescribed treatment will reduce risk of illness, and do not perceive there to be significant barriers to treatment adherence (e.g., they perceive that the benefits of adherence outweigh the costs). Moreover, this theory contends that a variety of other variables (e.g., patient demographics, mood factors, etc.) may influence these perceptions. In the HIV literature, various components of the HBM have been shown to be related to medication adherence and influenced by a variety of factors, including patient demographics and disease severity (Barclay et al. 2007; Gao et al. 2000). Barclay et al. (2007) assessed a variety of psychosocial, psychiatric, and drug use predictors in concert and found that components of HBM and self-efficacy were important predictors of antiretroviral medication adherence among younger participants. Among older participants, however, cognition remained the sole predictor of medication adherence.

Researchers have begun to develop theoretical models of social support, which has long been recognized to have a positive influence on medication adherence in a variety of illnesses (Becker and Maiman 1980; Greene et al. 1982), including HIV (Catz et al. 2000; Gonzalez et al. 2004). Studies aimed at delineating the manner by which social support influences medication adherence suggest that the relationship is indirect. Higher levels of social support are associated with reduced negative affect (e.g., depression, anxiety, and stress), increased spirituality, and increased medication-taking self-efficacy (either directly or indirectly through negative affect and/or spirituality). An important finding in these models is that medication-taking self-efficacy is directly related to medication adherence (Cha et al. 2008; Simoni et al. 2006). A positive relationship between the patient and health care provider also appears to have a beneficial impact on medication adherence and self-efficacy appears to mediate this relationship as well (Johnson et al. 2006). Ethnicity appears to be an important demographic variable that influences the relationship between social support and medication adherence. In a sample of HIV+ adults, a recent study from our laboratory found that patient satisfaction with healthcare provider was the strongest predictor of medication adherence among African–Americans beyond common factors (e.g., current drug use) that have been traditionally linked to medication adherence. Among

Caucasians, however, depressive symptoms and treatment related social support (e.g., friends assisting them with HIV-related care) were the strongest predictors of medication adherence (Thames et al. 2012). These findings lead us to conclude that strengthening and promoting social support (including the physician-patient bond) should be an absolute priority for increasing and maintaining optimal medication adherence. It is logical to opine that social support (e.g., receiving illness related support) may be an important mediating variable for individuals who present with cognitive dysfunction. These individuals may particularly benefit from having significant others around them reminding them to take their medications. Furthermore, the interaction between cognition and self-efficacy—now emerging as having a direct relationship to medication adherence—is also unknown. Individuals who are cognitively impaired may not be accurate in their reports of self-efficacy, and therefore this variable may be a poor predictor of adherence behavior for them. Preliminary work from our laboratory suggests that psychosocial variables (e.g., treatment related support) may buffer against the adverse effects of poor cognition on medication adherence (Arentsen et al. 2012).

More recently, a new theoretical framework, temporal self-regulation theory (TST; Hall and Fong 2007), has been developed. This model integrates social cognitive and neurocognitive factors. TST posits that individuals perceive a temporal dispersion between costs and benefits of health behavior. For example, for some unhealthy behaviors (e.g., smoking or drinking behavior), the benefits are more proximal than the costs. Individuals' ability to regulate behavior (self-regulatory capacity) in the context of this temporal dispersion of costs and benefits is a key and unique component in this theoretical model. Self-regulatory capacity refers to specific neurocognitive abilities (i.e., executive functions) and is thought to moderate the relationship between intention and action in health behavior. Hall and Fong (2007) found that frontal functioning moderated the relationship between intention and action for physical activity and dietary behavior (Hall et al. 2008). To our knowledge, this is the first integrative psychosocial model to include a neurocognitive component. Although this model has yet to be evaluated in the context of medication adherence to antiretroviral therapy, this may be a fruitful area of future research given the deleterious effect of HIV on executive functioning and the temporal dispersion of costs and benefits associated with adherence.

Conclusion

In summary, remarkable advances in antiretroviral therapy have led to a renewal of hope and a reconceptualization of HIV as a chronic disease rather than one that is inexorably terminal. Not unlike diseases such as diabetes or prostate cancer, increasingly patients will ultimately die *with* HIV rather than *from* HIV. But challenges remain. Comorbid conditions that initially placed some individuals at risk for contracting HIV, such as substance abuse and psychiatric illness, also pose considerable problems with regard to adherence. Cognitive disorders caused by the

virus compromise treatment adherence, which in turn aggravates those very cognitive difficulties. Concurrent factors such as normal and pathological aging, socioeconomic impoverishment, and systemic barriers impeding access to care yet further hinder attempts to understand and improve adherence behavior. Considerable progress has been made, particularly with regard to understanding risk factors associated with poor adherence, though interventions to address these risks remain understudied and insufficiently deployed. The challenge now is to implement translational, tailored interventions that incorporate knowledge gained through research into the clinical care of the multitude of patients who remain HIV infected.

Highlights

- Those living with HIV face the prospect of dealing with complex medication regimens and disease-related cognitive dysfunction.
- Cognitive dysfunction has been shown to disrupt medication adherence in HIV+ individuals.
- Executive function appears to be most centrally implicated in non-adherence.
- The consequences of non-adherence among HIV+ individuals is of significant concern to affected individuals and public health as a whole.

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Chapter 7
Alcohol Consumption and Self-Regulation

Barbara Mullan

Introduction

Self-Regulation and Alcohol

The history of alcohol and executive function has tended to concentrate on deficits in executive function, however, more recently self-regulation has been implicated in a range of alcohol use areas including binge-drinking, drinking studies in the laboratory and longitudinal studies of heavy social drinking. In this chapter an explanation of these different facets of this relationship will be explored.

Self-regulation refers to the capacity to exert control over cognition and emotion in order to organise and direct thinking towards enacting an intended behaviour (Baumeister et al. 2007). According to Hagger et al. (2009) self-regulation can be defined as "the propensity of a person to invest cognitive, emotional and behavioural resources to achieve a desired goal or outcome" p. 208.

Relevance of Self-Regulatory Capacity to Alcohol Consumption

As pursuing behaviour change is a key goal for health psychology, identifying the preceding factors of self-regulation that are malleable is extremely important (Taylor 2008). It has been contended that specific facets of self-regulation may be differentially predictive for different health behaviours. With regard to alcohol

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consumption, self-regulatory ability has been associated with the consequences of alcohol consumption, beyond actual alcohol consumption, such that self-regulation moderates the relationship between alcohol consumption and alcohol consequences (Neal and Carey 2005).

Executive Functioning

Self-regulation is often equated with executive function, both of which are implicated in the functions of the prefrontal cortex (Koechlin et al. 2003). Different definitions of executive function exist, ranging from parsimonious to more comprehensive. For example Miyake et al. (2000) identified with factor analysis that three components of executive function (mental set shifting, information updating and monitoring and response inhibition) were related but independent. Suchy (2009) has defined executive function as the biological efficiency that underlies self-regulation, "a multifaceted neuropsychological construct that…corresponds to the abilities to (1) reason and generate goals and plans (2) maintain focus and motivation to follow through with goals and plans (3) flexibly alter goals and plans in response to changing contingencies" (p. 106). In a more comprehensive definition, Giancola (2004) considered executive function to include self-monitoring, abstract reasoning, problem solving, planning, cognitive flexibility, impulse control and systematising of relevant material.

Executive functioning is particularly important for adolescents and young adults as these abilities are afforded primarily by the frontal lobe, and research in neuropsychology has shown conclusive evidence that the frontal lobe is the last part of the brain to develop and does not reach full maturity until approximately age 25 (Huttenlocher 1990).

Alcohol and Self-Regulation

Alcohol consumption contributes to a significant proportion of death, disease and injury (Pascal et al. 2009) and the high prevalence, particularly among young adults, is a worldwide concern (Moore et al. 1994; Naimi et al. 2003). Studies examining executive function processes and drinking behaviour have found differences between drinkers and non-drinkers. Of particular note, Lejuez et al. (2010) found that impulsivity was implicated in three stages of alcohol use: initiation of use, regular use and alcohol-related disorders. Further, poorer executive function can prevent improvement in substance use behaviours (including alcohol), further implicating executive function in the maintenance of alcohol dependence (Blume and Marlatt 2009). In addition, intoxicated individuals have been found to have poor inhibition performance on executive function tasks but not on other task components such as speed (Curtin and Fairchild 2003), implicating a bi-directional relationship.

Binge-Drinking and Executive Function

Binge-drinking is characterised by the intake of an excessive amount of alcohol on a single occasion (Norman et al. 1998). In Australia, the National Health and Medical Research Council (NHMRC) defines binge-drinking as the consumption of four or more drinks in one session (NHMRC 2009). The relationship between executive function and binge-drinking has been relatively well supported (e.g., Goudriaan et al. 2007; Hartley et al. 2004). One of the first studies to consider the relationship between executive functioning and binge-drinking was conducted in 50 heavy drinking college students (Blume et al. 2000). Better Wechsler Memory Test scores along with greater negative awareness of the consequences of drinking (but not other executive function measures) were related to greater awareness of the consequences of drinking, suggesting that short-term memory may be important in motivating change in binge-drinking behaviour. This study is noteworthy as it was one of the first to show poor executive function to be associated with motivational elements of behaviour. Furthermore, it appears that executive function may not only impact alcohol consumption directly, but also through more planned and intentional factors. In another study investigating executive function and motivational predictors of social drinking in young adults (Fadardi and Cox 2008), it was found that both maladaptive motivation and greater cognitive biases were predictive of alcohol consumption, further emphasising the importance of addressing both cognitive components of behavioural processes as well as motivational elements in interventions.

Mullan et al. (2011) found that moderate drinkers had greater inhibitory control than non-drinkers, implying that avoiding a binge-drinking session requires greater inhibitory control that avoiding alcohol completely or having more than four drinks. Mullan et al. (2011) conclude that in line with self-control theory, the superior inhibitory control exhibited by moderate drinkers may be the result of constant restraint. Other research has suggested that self-regulation may affect the implementation of intentions by inhibiting habitual responses such as the decision to have another drink, assisting in overcoming the influence of environmental triggers and by enabling the development of future plans (Palfai 2004). Further evidence supporting the link between executive function and alcohol comes from a study by Weissenborn and Duka (2003) who found binge-drinkers performed poorer in spatial working memory and in pattern recognition tasks than non-binge-drinkers. In addition, Heffernan and O'Neill (2012) also found selective memory impairments in binge-drinkers, but only for time rather than event-based prospective memory.

However, some of the research surrounding some executive function components such as working memory, and their role in binge-drinking remains inconclusive. For example, early correlational research into a sample of non-clinical 18–24-year-old social drinkers, found no relationship between cognitive performance and drinking behaviours (Bates and Tracy 1990). More recently, Parada et al. (2011) investigated the relationship between executive cognitive functions and binge-drinking in a sample of university students. Using laboratory-based measures, students who engaged in binge-drinking were less able to remember and manipulate information,

but displayed no differences in cognitive flexibility and planning to students who did not engage in binge-drinking.

It therefore appears that while executive functions are generally implicated in binge-drinking, evidence for the role of some components of executive function such as working memory still remains inconsistent. Still more research is needed to explore both in which aspects are most important and to determine the direction of causality (see below for more information).

Alcoholism and Executive Function

Adults diagnosed with alcohol dependence (Sullivan et al. 2000) and chronic alcoholics (Montgomery et al. 2012) have been found to have significant executive function deficits when compared to a control population. In particular, there is some evidence to suggest that when faced with a decision, at least a subgroup of substance dependent individuals tend to discount future consequences in the face of immediate benefits (Field et al. 2007; MacKillop et al. 2011; Mitchell et al. 2005). This decision-making deficit resembles decision-making patterns observed in individuals with lesions of the ventromedial prefrontal cortex (VMPC) (Bechara and Damasio 2002; Bechara et al. 2002). These VMPC lesions typically affect decision-making, with choices favouring immediate reward at the expense of goals or consideration of future consequences (Bechara et al. 1994, 1997). Substance dependent individuals may experience impaired VMPC functioning, and impairments may extend to other brain regions involved in decision-making, such as the amygdala. However, not all individuals displayed the same impairments, suggesting that individuals with substance dependence do not have uniform executive function impairments (Bechara et al. 2002). In addition, Bechara and Damasio (2002) acknowledge that it is unclear whether alcohol causes such impairments, or whether impairments can predispose individuals to alcohol abuse.

Bi-directional Relationship (Longitudinal Studies)

Research supporting the impact of alcohol consumption on executive functions indicates that the relationship is likely to be bi-directional. As Blume and Marlett (2009) state "when executive cognitive defects are identified among people abusing substances, it is generally difficult to sort out whether they represent the consequences of substance abuse or a pre-existing vulnerability for developing substance abuse" p. 118.

The bi-directional relationship between aspects of self-regulation and alcohol consumption was explored by Curtin and Fairchild (2003). When consuming alcohol individuals who had poor pre-existing central executive working memory had increased impulsivity and subsequently a reduction in behavioural inhibition.

This study provides evidence that pre-existing deficits in self-regulation can serve to amplify the effects of alcohol on other aspects of self-regulatory abilities, with the potential to create a bi-directional loop between alcohol consumption and self-regulation. This was consistent with research by Finn et al. (1999). Participants were assessed on working memory, sensation seeking and impulsivity while after having consumed no alcohol or up to two doses of alcohol. They concluded that alcohol increased impulsivity only for individuals low in working memory. However, family history of alcoholism was not associated with impulsivity, suggesting that these effects are attributable to self-regulation rather than other factors in alcoholism that may be passed down genetically or environmentally.

Muraven and colleagues (Muraven 2010; Muraven et al. 1999) have demonstrated support for the direction of effect from self-regulation to alcohol consumption. The first study (Muraven et al. 2002) explored self-control and alcohol. Male social drinkers had to either exert self-control by suppressing thoughts, while the control group completed difficult math problems instead. They then took part in a pseudo taste test, where the actual measure of interest was the amount of alcohol consumed. Individuals who suppressed their thoughts consumed more beer and achieved higher blood alcohol content than control participants. The study also found that individuals higher in trait temptation to drink consumed more after suppressing their thoughts relative to those lower on this trait. The authors concluded by suggesting that alcohol consumption may be a function of both temptation to drink and self-control strength. In the second alcohol study from this research group (Muraven et al. 2005) daily changes in ability to self-regulate was the variable of interest. They found that on days where self-regulatory demands were stronger, individuals were more likely to drink more than they had planned. It therefore appears that fluctuations in regulatory capacity can impact on alcohol consumption.

Another study looking at alcohol-related consequences (D'Lima et al. 2012) found that general self-regulatory abilities predicted alcohol-related problems. However, this relationship was mediated by alcohol-specific self-regulatory abilities, such that individuals with high self-regulatory abilities had higher alcohol-specific self-regulatory abilities, and subsequently fewer alcohol-related problems. A recent review into the self-control model and health behaviours more generally included a short section on alcohol consumption (Hagger et al. 2009). The authors conclude that intentional models of health behaviour may only be relevant when people have sufficient self-regulatory capacity to act on their intentions. This conclusion is supported by the study from Australia reported above such that for individuals who intended to binge-drink, those with high planning ability or high inhibitory control were more likely to avoid doing so (Mullan et al. 2011).

There is also evidence to support an association between executive function and longitudinal consequences of alcohol consumption. Previous research has shown that acting without thinking has a stronger association with addiction symptoms than sensation seeking (Magid et al. 2007). One longitudinal study investigated the association between development of prefrontal executive function and subcortical motivational brain regions, and their impact on sensation seeking and acting

without thinking over 3 years (Romer et al. 2011). They found that increases in executive function were associated with both increases in sensation seeking and decreases in thinking without acting. Another longitudinal study found that self-regulatory ability was associated with the consequences of alcohol consumption in young adults one-year later (Hustad et al. 2009).

Together this evidence suggests that executive function affects a person's ability to restrict alcohol consumption, and that alcohol consumption can further reduce executive functioning, which has the potential to create a vicious cycle. However, carefully designed interventions that look at both alcohol consumption and executive function have the potential to be successful, which is further explored below.

Direction of Relationship (Laboratory-Based Studies)

Support for a bi-directional relationship between self-regulation and alcohol consumption is also found in laboratory-based studies. Recent research has found that in alcohol consumers, exposure to alcohol cues can activate attentional biases and subsequently disrupt behavioural control (Weafer and Fillmore 2012), suggesting that associations learnt as a result of drinking can lead to reduced executive functioning and less regulation of subsequent drinking.

Mixed results have, however, been found for the role of alcohol consumption in executive function abilities. For example, Richards et al. (1999) found that the consumption of alcohol in a laboratory setting did not influence delayed discounting responses, but argued that this may have been due to methodological problems. Weissenborn and Duka (2003) also investigated the effect of alcohol consumption on laboratory cognitive tasks, and found that compared to a placebo, a blood alcohol concentration of 1.06 g/l impaired performance on planning and spatial recognition tasks, but not pattern recognition or spatial working memory. In another study, blood alcohol concentrations of 0.4 g/kg led to impairments on executive function tasks such as planning, prioritisation, creativity and adaptability measured using a virtual reality postage-based task, however, ability to choose between two or more alternatives based on prior knowledge was not impaired.

Curtin and Fairchild (2003) experimentally investigated the effects of alcohol intoxication on both evaluative (i.e. monitoring the need for control) and regulative (implementing control) control processes, as well as behaviour. Control processes were measured both with the Stroop task and electroencephalographic (EEG) recordings. Individuals who had consumed alcohol did not have generalised impairments in evaluative control, but rather a specific impairment on incongruent Stroop trials which required inhibitory control suggesting that alcohol can impact regulative control processes. Furthermore, EEG recordings of the parietal P3 revealed that both groups were able to extract the relevant information from all trials with no time delays. However, performance of two frontal lobe areas implicated in switching from automatic to controlled processes and working memory function was significantly reduced, suggesting that alcohol consumption can affect executive processes such as inhibition and regulatory control.

The lab-based literature suggests that there is likely an alcohol consumption-executive function relationship but much is not yet known. Extensive future research into both the specific aspects of executive function that are implicated in binge-drinking, and vice versa is warranted. In addition, the literature would benefit from an exploration of the moderators and mediators of this relationship.

Alcohol and Brain Damage

Rats typically sustain brain damage from the death of neurons and experience-related cognitive deficits after sustained heavy drinking (Crews and Nixon 2009). Similarly in humans, heavy alcohol consumption has been associated with frontal lobe shrinkage which is in excess of the normal ageing process (Kubota et al. 2001). A review of structural and functional changes as a result of alcohol abuse found that damage to the cerebrum and cerebellum due to alcoholism impacted frontal lobe functioning, and disrupted the fronto-cerebellar pathways, thus accounting for the cognitive effects of alcoholism, including executive dysfunction (Sullivan and Pfefferbaum 2005). Furthermore, Sullivan et al. (2000) found that no consistent pattern of deficit with respect to lateralised functions of the cerebral hemispheres emerged. In particular, executive functions, whether assessed with verbal or nonverbal material, was impaired in alcoholics when compared to non-alcoholics, however, alcohol consumption was more closely associated with motor impairments than impairments in cognitive functions such as executive function.

There is also evidence that damaged brain regions may undergo neurogenesis during periods of abstinence, suggesting that these changes are not necessarily permanent (Kubota et al. 2001; Sullivan and Pfefferbaum 2005). This change to executive function in alcoholics has implications for the treatment of alcoholism, as given the bi-directional relationship between alcohol and executive function, such neurogenesis may serve to increase self-regulatory capacity, thus enabling individuals to better restrict alcohol intake (Blume and Marlatt 2009), potentially leading to further neurogenesis and improved outcomes. The impact of executive function deficits when individuals with substance abuse first enter treatment, and the impact of different treatments on executive function deficits in this population therefore need further exploration.

Alcohol and Measurement Issues

One of the main issues to consider when exploring self-regulation is that the results may vary depending on whether paper-based or computer-based reaction time measures are used. Below is a summary of this literature, divided into these two areas, followed by a synthesis of the findings.

One longitudinal study into heavy drinking American college students with measurements points at 1, 6 and 12 months explored changes in alcohol consumption, alcohol related consequences and self-regulation. In this study the Short Self–Regulation Questionnaire (SSRQ) was used, which is designed to quantify an individual's ability to self-regulate behaviour in seven self-regulation factors, and has demonstrated strong internal consistency (Neal and Carey 2005). Hustad et al. (2009) found that participants' ability to self-regulate predicted base line alcohol-related consequences, as well as subsequent change in these consequences. In addition, change in self-regulation over 12 months was associated with changes in self-reported alcohol consumption. They concluded that self-regulation both acts as a protective factor from alcohol-related consequences, as well as promoting a reduction in actual alcohol use.

Given the nature of addiction, behaviour tends to occur despite intentions otherwise and outside conscious awareness (McCusker 2001). For example, Hall et al. (2006) conducted a study using the Stroop task to predict health risk and health risk behaviours, including alcohol consumption. They found that behavioural inhibition (as measured by errors on the Stroop task) predicted alcohol consumption above general cognitive function (as measured by the Peabody Picture Vocabulary Test-Revised; Dunn and Dunn 1981) and demographics variables of age, gender and education. McCusker (2001) has therefore argued that computer-based reaction measures such as the Stroop task are more appropriate than paper-based measures for this research area. These measures are beneficial as they assess the actual processes rather than perceptions of these processes, are less demanding as are not directly asking for behaviour information, and can access cognitive components that the individual is not explicitly aware of (Stacy 1997). In addition, Muraven et al. (2002) suggested that in the area of alcohol, methods which assess cognitive biases using reaction-based measures were better than those using self-report as they allow bias-free measurement.

Many reaction time measures support the executive function-alcohol consumption relationship. For example, Mullan et al. (2011) found that planning ability and inhibition control moderated the relationship between intention and behaviour such that for individuals who intended to binge-drink, those with high planning ability or high inhibitory control were more likely to avoid doing so. De Boer et al. (2011) investigated two aspects of self-control: control over initiating a response and control over inhibition or preventing a response, and found alcohol consumption was associated with poor response inhibition rather than initiation. Together these studies suggest that inhibition has a function in controlling alcohol consumption, which has implications for how interventions are designed.

However, some research using cognitive measures of self-regulation has not found consistent support for the impact of alcohol consumption on self-regulation. A systematic review and meta-analysis into the impact of heavy social drinking on executive function was recently published (Montgomery et al. 2012). In this study the authors identified seven studies which met their inclusion criteria. However, the mean effect size of executive function in social drinking was not significant. They however also conducted a study (reported in the same paper) that did show executive function differences between heavy and light drinkers.

Bates and Tracy (1990) used measures of memory, concept formation, abstract reasoning and visio-spatial skills, however, neither alcohol use in general nor excess alcohol consumption were linked to executive function. Hartley et al. (2004) explored the association between performance on computer-based executive function and memory tasks and binge-drinking. For executive function tasks, associations with binge-drinking were found for planning ability, but not for spatial working memory or mental flexibility. Binge-drinking was also associated with sustained attention and long-term memory recall but not pattern or spatial recognition memory. However, the results of this study must be interpreted with caution given their extremely small sample size.

In an attempt to identify the specific executive function components that are inhibited in alcohol users, Rossiter et al. (2012) used a modified version of the Go/No-Go task that was able to separately measure the effects of immediate punishment and delayed reward using monetary incentives on ability to respond and to inhibit responses to stimuli. In harmful drinkers who were at risk of developing alcohol dependence, impulsivity was not hampered by possible punishment, such that they were less sensitive to punishment compared to non-hazardous drinkers. However, harmful drinkers were sensitive to delayed reward, suggesting a possible avenue for future interventions.

Thus the evidence from cognitive- and paper-based tasks is mixed. A more systematic approach is needed, as many paper-based and cognitive-based measures of self-regulation are used, and research exploring the most appropriate measures is very limited.

Modification of Self-Regulation in Alcohol Studies

The mounting evidence suggests that if self-regulation can predict alcohol consumption, then interventions should aim to increase self-regulatory ability. Palfai (2004) has explored self-regulation within the context of targeting alcohol consumption, and acknowledges that automatic aspects of self-regulation play an important role in pursuing health goals, but are often downplayed in the literature compared to conscious top-down elements of decision-making. Indeed, interventions have been successful in training self-regulation in hazardous drinkers using the Alcohol Avoidance Task (Hagger et al. 2009).

However, executive function appears to have a strong genetic component. For example, Friedman et al. (2008) compared performance on three aspects of executive function (response inhibition, working memory and set shifting) in fraternal and identical twins. They found that executive function was almost entirely accounted for by general and specific genetic factors, suggesting both that executive function abilities are highly heritable and that environmental influences are limited. Such research suggests little room for interventions aimed at improving executive function.

Yet despite evidence of a strong genetic component, there is also mounting evidence that self-regulation and executive function are malleable, leading to

changes in alcohol consumption. A recent model of self-regulation suggests that self-regulation use can lead to a temporary 'depletion' of resources, and subsequently poorer self-regulation. In particular, individuals who attempted to suppress thoughts (Christiansen et al. 2011; Muraven et al. 2002), or engaged in self-control in other aspects of their life (Muraven et al. 2005) subsequently consumed more alcohol. However, with time and training self-regulatory ability can be improved. Studies have shown that repeated exercises of behavioural self-control such as reducing sweets, squeezing a handgrip, keeping a food diary and monitoring posture can lead to improved performance on executive function tasks (Muraven 2010; Muraven et al. 1999). This lends support to the notion that executive function is a muscle that can be strengthened. Executive function therefore appears malleable, but it is yet unclear whether improving executive function performance through training can improve health behaviours, although early indicators appear promising.

The majority of research to date has been lab based and predominantly involves some cognitive retraining followed by a pseudo 'taste test' which is actually the behaviour measure. Using this paradigm there is preliminary evidence that executive function can be successfully manipulated to induce changes in behaviour. For example, attention training has reduced harmful drinking up to 3 months later (Fadardi and Cox 2009). Houben et al. (2011) found that training working memory decreased alcohol consumption in the following month, while Houben et al. (2010) found decreased beer consumption following evaluative conditioning of beer with negative stimuli. Inhibition training has been effective in reducing alcohol intake in interventions as short as one session (Houben et al. 2012). It therefore appears that despite a strong genetic component, executive function can be improved with meaningful implications for alcohol consumption. It is possible that inherited levels of executive function may influence the responsiveness of individuals to self-regulation interventions, and future research is needed to investigate the interaction between pre-existing levels of executive function and performance on interventions.

Conclusion

The research into self-regulation and alcohol suggests that self-regulation may be very important both in predicting alcohol use and moderating the relationship between alcohol use and other important predictors of alcohol consumption. However, the literature is currently beset by operationalisation issues such as paper-based versus cognitive measures of self-regulation, a predominance of correlational studies, inconsistencies in the type of cognitive measure used and definitions of both self-regulation and alcohol consumption. These operationalisation issues are also confounded by the use of university students in many of the lab studies as with age, as not all individuals who engage in binge-drinking in adolescence will go on to continue to drink to excess, and not all research can account for different patterns of drinking over longer time periods. In addition the ability to explore the impact

of alcohol consumption on executive function is limited in this population, as the length of time and severity of alcohol use may be lower. Blume and Marlatt (2009) also highlight some important issues around interventions, as many current interventions into alcohol use appear to ignore the possibility of pre-existing executive function deficits and future research into this is needed. Moving forward, research needs to address this myriad of methodological issues. There needs to be greater cross-discipline collaboration, as research into executive function and alcohol consumption has been conducted in neuropsychology, abnormal psychology, health psychology and medicine, and these disciplines tend to approach research in different ways and a multi-disciplinary approach is needed.

Highlights

- The relationship between alcohol consumption and self-regulation is bi-directional.
- Although there is a genetic component to executive function, individual level self-regulation interventions have been moderately effective in changing alcohol consumption.
- Population-based interventions to improve self-regulation are now warranted, which may improve self-control over alcohol consumption at a more widespread level.

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Chapter 8
The Strength Model of Self-Control: Recent Advances and Implications for Public Health

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Introduction

Being able to control basic inner drives, impulses, and 'dominant' responses is a uniquely 'human' trait that enables people to pursue long-term goals at the expense of short-term outcomes. Such acts of *self-regulation* enable the initiation and maintenance of goal-directed behaviors that lead to adaptive outcomes such as success in the workplace and in education, stable and cohesive interpersonal relationships, less psychopathology, less anti-social behaviors, and better health (de Ridder et al. 2012; Metcalfe and Mischel 1999; Tangney et al. 2004; Wills and Stoolmiller 2002). This is extremely relevant to public health as the regulation of health promoting behaviors such as following a healthy diet, engaging in regular physical activity, consuming modest levels of alcohol, and refraining from smoking are all associated with reduced levels of chronic illness (de Ridder et al. 2012; Hagger 2010; Hagger et al. 2009). In contrast, failures in self-regulation are associated with a multitude of maladaptive consequences such as absenteeism in the workplace and at school, conflict and disharmonious personal relationships, personal debt, increased likelihood of antisocial behavior or criminality, lower levels of mental health and psychological wellbeing, and increased risk of illness (Steel 2007; Tangney et al. 2004). This has led psychologists and social neuroscientists to study the factors that lead to effective self-regulation of behavior, particularly impulse control and response inhibition, and those associated with poorer regulation (Baumeister and Heatherton 1996). Such an approach directed toward explaining the mechanisms and processes that lead to effective self-regulation with a view to develop means that may counter the deleterious effects of self-regulation failure.

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A prominent approach to the study self-regulation is derived from theories of self-control. Self-control can be considered a subset of self-regulation that encompasses individuals' ability to overcome their 'dominant' responses, such as impulses, habits, temptations, urges, cravings, and drives, in favor of a more distal goal that is adaptive but more effortful and time consuming (Baumeister and Heatherton 1996; Fujita 2011; Hagger et al. 2010a). Self-control can be conceptualized as a 'trait-like' or 'state-like' construct. Trait conceptualizations of self-control suggest that individuals vary in their general capacity to regulate their self and overcome the dominant responses (Baumeister et al. 2006; Tangney et al. 2004). This is contrasted with the state view of self-control on which ability to self-regulate is determined by factors in the environment such as the demands of the task or behavior (Baumeister et al. 1998; Muraven et al. 1998). Both conceptualizations are incorporated in the *strength* model of self-control, an approach that has led to a proliferation of research into self-control and associated processes and mechanisms (Baumeister and Vohs 2007; Baumeister et al. 2007; Hagger et al. 2010a; Muraven and Baumeister 2000).

In the strength model, self-control is conceptualized as a resource or strength which is limited and becomes depleted after a period of self-control 'exertion' (Baumeister et al. 1998; Muraven et al. 1998). The state of self-control resource depletion is considered a temporary one in which individuals will be less able to engage in tasks and activities that require self-control, but such capacity can be restored after a period of rest or recuperation. As its moniker implies, self-control is considered analogous to a muscle. Just as the force exerted by a muscle experiencing a constant workload over time wanes, so self-control resources become diminished when an individual works on tasks that require self-control. The state of reduced capacity for self-control has been termed *ego-depletion*. The model has received a considerable amount of attention in the social science literature over the past decade due to its intuitive appeal and generally robust findings (Baumeister and Vohs 2007; Baumeister et al. 2007). Importantly, the model has been adopted to explain the role of self-regulatory failure in public health contexts, particularly health promoting behavior (Hagger 2010; Hagger et al. 2009). In this chapter, we will provide an up-to-date overview of the basic tenets of the strength model of self-control, the mechanisms responsible for its effects, and associated hypotheses. We will also provide a contemporary overview of the model and its mechanisms, provide an up-to-date overview of recent developments and extensions of the model, outline its relevance to understanding public health issues, and detail some recommendations for practice and future research.

The Strength Model: Hypotheses and Evidence

According to the strength model, self-control resources are finite and become depleted after an individual engages in a task or activity that demands self-control for a period of time (Baumeister et al. 1998; Muraven et al. 1998). The

ego-depletion effect has been typically tested in laboratory settings using an experimental procedure, known as the *dual-task paradigm*. Participants are asked to engage in an initial task. Participants are randomized to an experimental group which receives a task that requires self control or a control group which receives a task that does not require self control. All participants then engage in a second self-control task in a different domain of self-control to the first. Performance on the second task represents the dependent measure of self-control capacity and, to the extent that performance on the second task is impaired in the experimental group relative to the control group, the researcher has sharp confirmation of the ego-depletion effect. A classic example of a dual task experiment was conducted by Baumeister et al. (1998) in the seminal work that predicated the ego-depletion effect. Participants were shown into a laboratory which was filled with the aroma of freshly baked cookies and seated behind a table on which was placed two plates of food: tempting cookies and bland radishes. Participants in the self-control group were asked to taste the cookies and leave the radishes while those in the experimental (ego-depletion) group were asked to taste the radishes only and leave the cookies. They were then asked to engage in a frustrating figure-tracing task that was rigged so as to be impossible to solve. Consistent with hypotheses, those who were asked to resist the cookies persisted for less time on the figure-tracing task than those able to taste the cookies. Participants had to exert considerable self-control in resisting the cookies which was hypothesized to deplete their resources leaving their capacity impaired for the figure tracing task.

The ego depletion effect has been tested in numerous studies using self-control tasks from in a number of different domains including impulse suppression (e.g., handgrip strength task, Stroop colour naming task), cognitive processing (e.g., digit-span task), emotion suppression (e.g., active moderation of facial expressions when viewing emotion-evoking stimuli), through suppression (e.g., suppression of unwanted thoughts), social processing (e.g., resisting making racial or sexual stereotypes, engaging in demanding social interaction), controlling attention (e.g., vigilance tasks), and choice and volition (e.g., making consumer choices). These findings not only support the ego-depletion hypothesis but also corroborate a key corollary of the model that acts of self-control are governed by a unitary resource that generalizes to multiple domains.

We conducted a meta-analysis to synthesize the research on the ego-depletion effect. Out analysis revealed that the ego-depletion effect was medium-to-large in magnitude and consistent across task domains (Hagger et al. 2010a). Furthermore, the effect has been replicated in numerous behavioral domains including health (e.g., Friese et al. 2008; Martin Ginis and Bray 2011; Teunissen et al. 2012), education (e.g., Bertrams et al. 2011; Price and Yates 2010), occupation (e.g., Chan and Wan 2012; Schmidt and Neubach 2010), financial management (e.g., Boucher and Kofos 2012; Oaten and Cheng 2007), social interaction (e.g., Ciarocco et al. 2012; DeWall et al. 2010; Gailliot and Baumeister 2007; Tyler 2008), and consumer behavior (e.g., Hofmann et al. 2008; Sultan et al. 2012; Usta and Häubl 2011). Overall, a considerable amount of research has supported the basic premise of the ego-depletion effect and the primary tenet of strength model.

Additional Hypotheses

The strength metaphor has also given rise to several additional hypotheses consistent with self-control as a unitary, limited resource. These include the tenet that the depletion of self-control strength is a relatively short-term phenomenon and can recover relatively quickly after a period of rest or recovery, the premise that when resources are scarce individuals will conserve their self-control resources for times of extreme need, and the proposal that training on self-control tasks can improve self-control capacity and promote better self-control under conditions of ego-depletion. We will visit each of these hypotheses in turn and evaluate the evidence to support them.

The Recovery Hypothesis

In keeping with the self-control-as-a-muscle metaphor, it has been proposed that once depleted an individuals capacity for self-control will be reduced, as indicated by impaired performance on self-control tasks post-depletion, unless sufficient rest is provided to for recovery. To date there is only one study that has tested this hypothesis. Tyler and Burns (2008) revealed that an extended period between the two tasks in a two-task paradigm led to much better second-task performance among the rested performers relative to those not given a rest. We endeavoured to provide additional support in our meta-analysis by examining whether longer or shorter periods between tasks in the dual task paradigm would affect self-control performance (Hagger et al. 2010a). Specifically, we examined whether studies that required participants to complete questionnaires or engage in filler tasks between the two tasks, indicating increased recovery time, led to better performance on the second task compared to studies in which participants who did not complete questionnaire tasks or fillers. Our results did not reveal any differences, although it must be acknowledged that ours was a relatively crude measure of the time gap between tasks. So, overall, only Tyler and Burns' study has supported this hypothesis and there is clearly a need for additional research to corroborate the role of recovery period in the replenishment of self-control resources.

Interestingly, the recovery of self-control resources does not seem to be confined to rest alone. In a second experiment, Tyler and Burns (2008) subjected participants to a 'relaxing music' condition relative to a 'quiet rest' condition between tasks in a dual-task paradigm experiment. Results revealed that participants in the relaxation condition also performed better on the second task relative to the 'quiet rest' participants. Similarly, a recent study demonstrated that engaging in mindfulness meditation showed no impairment of self-control performance on the second self-control task after depletion while depleted participants demonstrated the expected depletion pattern (Friese et al. 2012). These results suggest that replenishment of self-control resources is also dependent on the quality or nature of that recovery protocol as opposed to rest alone. Both these findings appear to

be consistent with the strength metaphor, as both time and quality of recovery are considered important to the replenishment of strength.

One of the issues arising from the analysis of the relatively limited data available on the recovery hypothesis, is the fact that tests of the ego-depletion effect in the confines of the strength model have generally been confined to tasks of a very short-term duration. Our analysis of dual-task paradigm tests of the model has revealed that the typical duration of self-control tasks was less than 10 min with very little variation and this duration was only weakly and non-significantly related to the ego-depletion effect size. Research in vigilance tasks and the cognitive fatigue literature have given some indication that serious decrements in task performance occur after long-term engagement in tasks typically associated with requiring self-control, there has, to date, been no research examining the effect of self-control task duration on the extent of depletion. In addition, research should also investigate whether variations in the length of the recovery period is proportional to the extent of the recovery of self-control resources. This seemed to be the finding of Tyler and Burns who found that varying rest periods led to incrementally better performance on the second self-control task. This should be a priority for future research examining the effect of recovery on self-control resource depletion.

The Conservation Hypothesis

Initial tests of the ego-depletion effect implied that self-control capacity was impaired because resources were near exhaustion. Subsequent tests have suggested that depletion of self-control resources is really only partial, meaning that resources are only scarce and lacking in availability rather than near to exhaustion. This implies that depletion is really due to an unwillingness or inability to commit remaining resources to additional demands post depletion. Testing this notion, Muraven et al. (2006) revealed that depleted individuals informed that they would be required to engage in future self-control tasks performed significantly worse on follow-up self-control tasks compared to participants who received no information on future tasks. This was proposed as evidence that individuals are motivated, consciously or not, to conserve self-control resources for future demand.

Consistent with the conservation hypothesis and the partial depletion rather than near exhaustion proposal, it was hypothesized that individuals should be able to commit their scarce self-control resources to performing self-control tasks post-depletion provided they have sufficient motivation or incentive to do so. Supporting this notion, a number of studies have indicated that providing external rewards or personal incentives to participants to perform subsequent self-control tasks leads to better self-control under depletion compared to participants not furnished with any motivational contingency (Moller et al. 2006; Muraven 2008; Muraven et al. 2008; Muraven and Slessareva 2003). The mechanism responsible for these findings is unclear. Research has suggested that self-efficacy and confidence on tasks

is not related to performance on self-control tasks post depletion (Wallace and Baumeister 2002), so it appears that confidence toward performing the tasks is unlikely to be the mechanism. Muraven and Slessareva (2003) claim that the motivational research does support an alternative explanation that self-control resource depletion is really caused by a lack of motivation because the effects of the incentives are confined to depleted and not non-depleted participants, and argues that it is motivation commit the resources that determines performance on self-control tasks under depletion rather than the effect being mediated by motivation per se. However, the role of motivation in self-control resource depletion remains a controversial one, and there is still debate as to whether self-control is really due to a unitary, limited resource at all. This will be revisited in the *Mechanisms and Processes* section of this chapter.

The Training Hypothesis

There now exists substantial evidence that training or practice on self-control resource depletion can lead to better self-control performance over time. According to the model, training self-control should improve self-control task performance under conditions of depletion by improving the efficiency or availability of self-control resources. A number of studies have used innovative means to train self-control strength and examine the effects on self-control task performance under depletion. Research has shown that engaging in short-term (e.g., controlling speech, using the non-dominant hand, or even regular rinsing with full-strength mouthwash) or long-term (e.g., engaging in programs of exercise, study, or financial management) lead to improved performance on self-control tasks under depletion in the context of a dual-task paradigm (Hui et al. 2009; Muraven et al. 1999; Oaten and Cheng 2006a, b, 2007; Sultan et al. 2012).

Interestingly, our meta-analysis revealed that long-term training studies have been shown to be more effective than short-term training in improving self-control capacity and also on behaviors beyond the experimental tasks within the dual-task paradigm such as dieting, smoking, and exercise (Hagger et al. 2010a). Such research is extremely appealing to those interested in developing behavior-change interventions to promote adaptive outcomes like weight loss or sound financial management. The research implies that training the self-control 'strength' is effective in producing better self-control performance. The mechanisms behind these effects remain elusive and also the longevity of the training effects has yet to be ascertained. Furthermore, it is unclear why some training is effective in improving self-control resource depletion but individuals who are engaged in chronic self-control tasks such as dieters seem to be more vulnerable to self-control resource depletion. It is possible that training needs to involved short-term, discrete, successful performance of self-control tasks to yield important improvements in self-control capacity while long-term, chronic, and unsuccessful self-control experiences undermine self-control capacity (Hagger et al. 2010a).

Trait Self-Control and Self-Control Strength

Much of the literature on self-control from the resource depletion perspective has focused on the short-term 'state' depletion of self-control resources in which environmental demands on self-control, manifested in the initial task in dual-task procedure experiments, lead to immediate failure on self-control tasks. However, much of the self-control literature views self-control as a trait-like construct: a generalized capacity that is stable and enduring (de Ridder et al. 2012; Metcalfe and Mischel 1999; Mischel et al. 1989; Tangney et al. 2004; Wills and Dishion 2004; Zabelina et al. 2007). In an attempt to reconcile these literatures, Baumeister et al. (2006) indicate that trait self-control can be unified with the strength model in the sense that trait self-control acts as a moderator of the ego-depletion effect. In other words, individuals may vary in their overall capacity for self-control and this may lead them to be less vulnerable to the state depletion of self-control resources by the tasks typically used to deplete resources. Research examining this moderating effect of trait self-control has been relatively inconclusive, with some studies revealing the moderating effect and others returning null results (Hagger et al. 2010b). There is definitely scope for future research that systematically examines the moderating role of trait self-control on self-control resource depletion and, most importantly, examining the extent to which high self-control provides a 'protective' effect from the deleterious effect of depletion on self-control task performance.

What is a Self-Control Task?

While the strength model has received considerable support, the model is not without criticisms and controversial debates. Prominent among these debates is what, exactly, constitutes a self-control task. In the original conceptualization of the strength model Baumeister et al. defined self-control in terms of the capacity to overcome impulses, desires, and temptations in keeping with previous reviews of the literature. Self-control was also considered perhaps a more narrow concept that a more global term, self-regulation, which tends to encompass impulse control as well as more global, sustained goal-directed behavior requiring effortful action at the expense or suppression of alternative courses of action (for a complete review see Fujita 2011). The tasks adopted in tests of the strength model usually match closely with the definition provided by Baumeister et al.'s (1998) original conceptualization and our meta-analysis demonstrated that the tasks typically used in the literature on the strength model fall into the distinct categories outlined previously. However, some studies have adopted self-control tasks within the dual-task paradigm which have tended to 'stretch' the definition of a self-control task in that they tap processes originally considered to lie outside the definition of self-control. This is because such tasks require the application of a set, well-learned algorithm rather than having to overcome well-learned response or impulse. For example, some researchers have adopted complex math or computational tasks as depleting task (e.g., Tyler and Burns 2008;

Webb and Sheeran 2003; Wright et al. 2003). Such tasks were originally considered not depleting by Baumeister et al. and were even used as the 'non-depleting' task in the dual-task paradigm control condition (Muraven et al. 1998). Research adopting such depleting tasks claim otherwise and suggest that such tasks tap self-control because they are tedious, effortful and, most importantly, require a person to overcome the urge to quit because of their arduous nature or require complex multiple operations (e.g., division and subtraction in quick succession) rather than single operations.

We recognized this distinction in our recent meta-analysis and even performed a moderator analysis for the ego-depletion effect for studies adopting depleting tasks in the dual task paradigm that adhered to the strict Baumeister definition of self-control compared to those using 'easy or difficult' tasks according to the more elaborated definition. Comparison of these moderator groups revealed no significant difference in the effect size leading us to conclude that both types of task were equally effective in inducing depletion. In conclusion, we suggested that "it seems that effect of self-control depletion on task performance may apply to a broader set of tasks and processes than originally proposed, including difficult or complex tasks" (Hagger et al. 2010a, p. 500). We developed a taxonomy of tasks used a depleting and dependent tasks in dual-task paradigm experiments representing the different domains of self-control, and interested readers are encouraged to read the supplementary materials to our meta-analysis for details (Hagger et al. 2010a, Appendix A).

However, a question still remains as to the characteristics for these tasks necessary to induce self-control resource depletion. For example, how long does an individual have to engage in a self-control task in order to induce depletion? What is the most effective way of developing a 'control' version of a task? Recent research has begun to tackle these kinds of questions. For example, a recent study indicated that performing an attention control task similar to that used by Muraven et al. (1998) for 2 min was insufficient to impair performance on a subsequent anagram-solving task, but performing the task for 4 min or longer was sufficient to induce depletion (Vandellen et al. 2012). Further research is needed to support these findings, but they provide useful initial information to support the premise that task selection and duration are important features of tasks that make them sufficiently demanding of self-control resources to induce ego-depletion.

Mechanisms and Processes

Glucose

Central to understanding the mechanism that governs self-control 'strength' within Baumeister et al.'s (1998) model is what form, exactly, does the resource take. From the outset of the tests of the model, the resource was defined in metaphorical terms as a form of 'energy' or 'strength', but this definition is unsatisfactory in terms of identifying what it is that become depleted in dual-task experiments. Baumeister et al. (1998) were confident from their initial proposal of the model

that the resource was more than mere metaphor and was associated with some physiological component: "(it is) implausible that ego depletion would have no physiological aspect or correlates at all" (p. 1263). Gailliot et al. (2007) proposed that a possible candidate for the resource was glucose. Specifically, they proposed that self-control tasks would be associated with the utilization of glucose in the brain as a metabolic fuel when performing self-control tasks and that depletion would be associated with falls in the availability of glucose for brain processes. They demonstrated that depletion coincided with falls in blood glucose levels and that supplementation of glucose moderated the ego-depletion effect. However, these results were disputed by authors who demonstrated that the data for the falls in blood glucose were inconclusive and that there was no evidence for fluctuations in glucose availability in the brain (Beedie and Lane 2011; Kurzban 2010).

Following up this research, we have recently demonstrated that the effects of glucose supplementation on attenuating self-control resource depletion may be perceptual rather than metabolic (Hagger and Chatzisarantis 2013). Following exercise physiology research demonstrating that the mere presence of glucose in the oral cavity is sufficient for improving physical endurance, we proposed that tasting, but not ingesting glucose, would lead to individuals overcoming the deleterious effects of self-control resource depletion. We adopted a novel 'mouth rinse' procedure in which participants tasted, but did not ingest, either a glucose solution or an artificially sweetened placebo solution, randomly assigned, in between the two self-control tasks in a dual-task paradigm. Results were consistent with Gailliot et al.'s (2007) findings for glucose supplementation such that self-control performance under conditions of depletion was significantly better when participants rinsed their mouths with glucose relative to placebo and that the effect was confined to depleted participants. A possible mechanism for this finding is that oral receptors exclusively sensitive to glucose send afferent signals to brain regions associated with reward, motivation, and conflict monitoring. The results led us to conclude that, because the solutions in Gailliot et al.'s experiments passed through the oral cavity, the effects of glucose supplementation in attenuating ego-depletion may have been due to the sensing of glucose rather than the metabolic explanation provided by Gailliot et al. Therefore, a question exists as to whether glucose is a suitable candidate for the self-control resource in the strength model.

Neural Correlates

Researchers have also aimed to identify neural correlates of effective self-control with the goal of unveiling the regions of the brain that govern effective self-control and become inhibited under ego-depletion. Research adopting neuroimaging techniques such as electroencephalography and functional magnetic resonance imaging have shown that ego-depletion coincides with reduced activity the anterior cingulate cortex (ACC). The ACC has been found to govern a number of processes important for self-control such as conflict monitoring (Botvinick et al. 2004; Inzlicht and Gutsell 2007) and the need for cognitive control (Heatherton 2011; Heatherton

and Wagner 2011; Lorist et al. 2005). Research has shown that engaging in tasks that require self-control, such as the Stroop color-naming task (Leung et al. 2000) and the handgrip strength task (Liu et al. 2003), is associated with activation in the ACC. In addition, EEG studies have found an attenuation of activity in the neural pathways associated with conflict monitoring, the process by which individuals detect and respond to mismatches in actual and intended responses, during performance of self-control tasks under conditions of depletion and mental fatigue (Inzlicht and Gutsell 2007; Lorist et al. 2005). Activation of the conflict-monitoring system is associated with peaks in error-related negativity (ERN), an EEG waveform isolated in the ACC in neuroimaging studies (van Veen and Carter 2002). Weaker ERN signals have been found in participants performing a Stroop task after the prior depletion of self-control resources compared to non-depleted controls (Inzlicht and Gutsell 2007). It seems that the ACC may play an important role in mediating performance on tasks requiring self-control.

In contrast, a recent fMRI study examining the regions of the brain that may be implicated in self-control resource depletion revealed deficits in the dorsolateral prefrontal cortex (DPFC) but no deficits in ACC activity (Hedgcock et al. 2012). The DPFC is responsible for signaling the need for cognitive control rather than conflict monitoring (Heatherton and Wagner 2011). The authors suggested that this region is the most likely candidate to be involved in self-control depletion rather than the ACC, suggesting that it is control rather than conflict monitoring which may be the most important component. This has been suggested in reviews of the neural correlates of ego-depletion (Heatherton 2011; Heatherton and Wagner 2011). At present, the converging evidence from neuroimaging research seems to suggest that both mechanisms may be involved and it is possible that self-control tasks may differ in the extent to which each neural system contributes to controlling the process. If this is the case, then it raises two questions. First, is effective self-control governed by two separate systems such that deficits in either one, or both, leads to ego-depletion? Second, if different self-control tasks are controlled by a separate system, what implications does that have for self-control being determined by a generalized, unitary resource that applies to all tasks? Clearly, this has implications for the strength model. Is it possible that a single resource can account for two separate neural processes that may be involved in self-control performance? We look to further investigations using neuroimaging techniques for different self-control tasks to shed further light on the brain processes associated with self-control resource depletion from the perspective of the strength model.

Recent Findings: Individual Differences and Cognitive Explanations

Recent research has focused on identifying factors that moderate the ego-depletion effect in an attempt to unveil potential boundary conditions and mechanisms for the effect. The findings have raised questions as to whether the effect is due to a limited

resource and may, instead, be moderated by other cognitive processes. For example, recent studies have revealed that individual differences in beliefs about self-control (Job et al. 2010) and procrastination (Fitzsimons and Finkel 2011), expectancies of the effort required by self-control tasks (Vandellen et al. 2012), and the provision of consistent and misleading feedback regarding the state of self-control resources (Clarkson et al. 2010) moderate the ego-depletion effect. In addition, research has indicated that actual depletion need not take place, and that depletion effect can also be 'acquired' by taking the perspective of someone experiencing self-control resource depletion (Ackerman et al. 2009). These findings suggest that an alternative mechanism for self-control failure may be due to cognitive beliefs about the nature of self-control rather than to the depletion of a finite unitary resource controlled by a physiological mechanism such as glucose availability.

The research groups behind these studies suggest that their findings indicate that self-control resource depletion may be a function of both cognitive processes and a limited resource related to a kind of strength or energy. The results of these studies do not, on their own, rule out the possibility that self-control is governed by a unitary resource, but they do provide evidence that picture is one that is more complex and multiple processes may be involved. For example, it is possible that beliefs play a substantial part in determining a person's self-control capacity on tasks, and that may be a limiting or facilitating factor when it comes to resource availability. These studies are indicative of the intense and innovative research currently being conducted in the area of self-control and, in particular, on the strength or limited resource model. It is clearly an exciting time for research on self-control and the ongoing attention paid to this area will inevitably lead to further evidence that may yield a more elaborated model of self-control that likely encompasses a limited resource model alongside other perspectives.

Implications for Public Health

Self-regulation is a key variable when it comes to promoting the uptake and maintenance of behaviors associated with good health. Research has demonstrated that high levels of self-control are consistently associated with health-related behaviors (De Ridder et al. 2008; de Ridder et al. 2012). This is because many health-related behaviors such as following a diet low in saturated fat, sustaining physical activity regimen, adhering to proscribed medication, cutting down on alcohol, quitting smoking, and attending appointments to see medical specialists, all require individuals to engage in long-term, goal directed behavior at the expense of short-term gains or resist some sort of immediate temptation or urge (Hagger et al. 2009; Hall and Fong 2007; Hofmann et al. 2008). This could be the temptation to opt for a sedentary pastime (e.g., watching television) instead of going out to jog after a hard day's work or resiting the urge to smoke if trying to quit smoking. Good self-control also means that individuals will likely be successful in regulating their behavior without the need for any external reinforcement or contingency: they will *self-regulate*. This

is important as health interventionists aim to increase the number of people engaging in health related behavior and reduce the financial and logistical costs of providing constant reinforcements or reminders to persuade and cajole individuals into engaging the health-promoting behaviors and avoid health-compromising behaviors.

From the perspective of the strength model, current research has implicated state self-control as having an important impact on decision making with respect to health related behaviors such as physical activity (Hagger et al. 2010b) and eating behaviors (Hagger et al. 2009). This suggests that self-control resource availability may be implicated in the self-regulation of health behavior. Bolstering self-control is therefore likely to have substantive effects in boosting engagement in health promoting behavior and avoiding health-compromising behavior. Fortunately, research has demonstrated that practice and training on self-control can promote self-control on laboratory-based tasks (Hui et al. 2009; Muraven et al. 1999) as well as behaviors associated with good health such as diet, exercise, and alcohol consumption (Oaten and Cheng 2006a, b, 2007). A key recommendation for intervention designs is that simple self-control exercises can have a facilitative effect on behaviors that require self-control. To date much of the research on practice with self-control has used contrived behaviors such as controlling speech or using a non-dominant hand (Hui et al. 2009; Muraven et al. 1999). Such behaviors may be considered impractical or seemingly trivial, the success of the training in promoting better self-control notwithstanding, so research needs to be conducted into more practical means to train self-control. For example, we have recently conducted the trial of a mobile phone application which enables participants to engage in a self-control task (e.g., a Stroop color-naming task) on a regular basis and are prompted to do so by the phone. This has been successful in improving self-control performance after only 2 weeks. Future studies need to be conducted to examine whether such training has a long-term impact of health-related behavior. The current state of the literature suggests that self-control training will have a positive effect in boosting self-control performance and should be considered an element for inclusion in future health behavior-change interventions.

Conclusions

The strength model of self-control has received considerable attention in the literature due to its relative simplicity and intuitive appeal. Research in a wide variety of domains and tasks has supported the primary hypothesis of the model that self-control is governed by a unitary resource that is finite and becomes depleted after engaging in a period of self-control. There is also support for additional hypotheses that have emerged from the model including the recovery, conservation, and training hypotheses. The mechanisms responsible for the effect are yet to be fully elucidated and the precise nature of the proposed resource is still hotly debated with proposals of glucose and neural correlates receiving considerable attention in the literature. The model has important implications for public health, particularly with

respect to recommendations for interventions to boost self-control. Future research needs to elucidate the mechanisms that underpin self-control resources and focus on identifying effective and practical means to boost self-control in health behavioral contexts.

Highlights

- A substantive literature supports the conceptualization of self-control as a form of strength or energy that is finite and limits individuals' capacity on tasks requiring self-control.
- The state of self-control resources depletion is known as *ego-depletion*.
- Research also indicates that recovery time moderates the replenishment of self-control resources, the expectation of future self-control leads to a conservation of resources, and repeated practice on self-control tasks improves subsequent performance on self-control tasks.
- Recent research has identified potential moderators of the ego-depletion effect including beliefs about the nature of self-control and the sensing of oral glucose.
- Future research needs to provide evidence to support the efficacy of interventions incorporating training on self-control tasks to improve self-regulation of health-related behaviors and produce long-term outcomes relevant to public health.

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Chapter 9
Incentive-Based Interventions: Historical Context and New Directions

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For many years the major challenge in public health was preventing and treating infectious disease. Currently, in developed countries, that challenge has largely shifted from infectious to chronic disease. Thanks to vaccines and other advances in clinical and preventive medicine, many more people in developed countries die from chronic diseases such as coronary heart disease and diabetes than from infectious diseases. A major characteristic of many of these chronic diseases is that they have behavior as a proximate cause. Indeed, taking the U.S. as an example, unhealthy personal behaviors are estimated to account for approximately 40 % of premature deaths annually (Schroeder 2007).

Substantial empirical evidence demonstrates that unhealthy behavior patterns (e.g., overeating, lack of physical activity, smoking, and other drug abuse) are acquired and maintained through behavioral reinforcement processes (Schultz 2010). As such, they have certain characteristics (e.g., strong preference for: fats and sweets, more immediate over delayed rewards, and larger over smaller amounts) that may have served us well earlier in our evolutionary history but are less adaptive and even potentially toxic in our contemporary industrialized culture. When caloric intake is an issue of survival, fat and sugar are appropriately highly rewarding. Similarly,

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when the next meal makes the difference between life and death one might weigh more heavily a smaller immediate meal in lieu of the uncertain or delayed larger meal. These mechanisms lead to biases in decision making, that is, how we make choices. Clinical neuroscience studies indicate that limbic system activity in areas associated with midbrain dopamine systems underpin biases toward the more immediate and larger magnitude rewards while greater relative activity in frontal parietal regions are associated with choices toward longer-term options (Bechara 2005; McClure et al. 2004). While everyone is biologically prone to these biases to extent, membership in certain populations (e.g., less educated populations, those with substance use disorders) and certain environmental contexts (e.g., constraints on the availability of alternative rewards) increase the likelihood of biased responding to an extent that can undermine health (Bickel et al. 2007; Bradford 2010; Green et al. 1996; Higgins 1997; Jaroni et al. 2004).

Since these unhealthy behavior patterns are overrepresented in socioeconomically disadvantaged populations, they are also significant contributors to the unsettling problem of health disparities (Cutler and Lleras-Muney 2010; Higgins and Chilcoat 2009; Kumanyika 2012). The problems do not stop there, though, as the economic costs associated with these behavior patterns are staggering and shared broadly. In the U.S., for example, it is estimated that the direct annual medical costs of smoking exceed $90 billion, alcohol abuse costs approximately $25 billion, and overweight and obesity approximately $150 billion (Centers for Disease Control, Prevention, 2008, 2011; Finkelstein et al. 2009). Such disparities and associated economic burdens also appear to be growing (Adler and Newman 2002; LaVeist et al. 2011) and as such leave little question that more needs to be done to promote health-related behavior change in these challenging populations and circumstances.

One evidence-based approach to this challenge is the use of monetary incentives. This approach to behavior change is commonly referred to as contingency management, especially within the addictions field where the largest body of health-related incentives research has been conducted. Incentives are successful in changing a range of unhealthy behavior patterns in a variety of different clinical populations (Higgins et al. 2008, 2012). Incentive-based treatments systematically offer relatively immediate material rewards contingent on objective evidence of behavior change. A particularly noteworthy point about this approach is that it leverages the same behavioral processes and associated mechanisms that lead to health-related behavior problems (e.g., small, frequent, and relatively immediate rewards) to promote healthier choices (Knutson et al. 2001; McClure et al. 2004).

The use of financial incentives for changing health-related behavior dates back to the 1960s and the advent of behavior modification and behavior therapy with some of the earliest applications being in the areas of obesity and substance use disorders (SUDs) (e.g., Ferster et al. 1962; Miller 1975). However, as was mentioned above, the most systematic development of this treatment approach has occurred in the SUDs field. This chapter provides a brief overview of the development of the incentives approach, primarily using research on SUDs to illustrate its

methods and outcomes, while also discussing how incentives are being applied in other health-related areas.

Substance Use Disorders

Several seminal studies set the stage for the eventual development of incentives as a treatment strategy. In the early 1960s, initial studies using animals (see Schuster and Thompson 1969 for an early review) demonstrated that intravenous drug injections would function as unconditioned positive reinforcers (i.e., maintain arbitrary behavior) in otherwise normal, healthy laboratory animals. A large body of subsequent research demonstrated that most of the drugs that were abused by humans were also voluntarily self-administered by laboratory animals (Collins et al. 1984; Deneau et al. 1969; see also Johanson and Schuster 1981). Moreover, if provided unconstrained access to substances like cocaine, these laboratory animals would ingest the drug to the exclusion of basic sustenance and to the point of premature death (e.g., Deneau et al. 1969). What this research demonstrated was the fundamental role that the behavioral process of reinforcement played in driving repeated drug use and its associated adverse consequences. No special pathology was necessary to promote drug use and abuse, even in its most pernicious form. What the research also raised was a very fundamental question. If drug use and abuse was a product of relatively natural biological processes such that even everyday laboratory animals would partake, how might that same basic reinforcement process be brought into play in preventing or treating SUDs and similar problems (e.g., Higgins et al. 2004a)?

Some of the first studies examining the application of reinforcement principles to drug use among those with SUDs were conducted with chronic alcoholics residing on a residential research ward (Liebson and Bigelow 1972; Liebson et al. 1973; Bigelow et al. 1974; Griffiths et al. 1974). These studies demonstrated convincingly that drinking could be modified by systematically delivered behavioral consequences. After this demonstration that drug use was a modifiable behavior under highly controlled conditions, Miller (1975) conducted the first randomized controlled trial of incentives in the treatment of SUDs. A group of 20 alcoholic homeless men were randomly assigned to receive social services as usual or social services contingent upon objectively verified abstinence from alcohol. Contingently received services successfully reduced public drunkenness arrests and increased days of employment as compared to the control condition.

In the late 1970s and early 1980s incentives research on SUDs continued in the form of small proof-of-concept studies, especially in a series of studies by Bigelow et al. (1976) that demonstrated that alcoholics would comply with a regimen of disulfiram therapy (a medication used to treat chronic alcoholism) to earn back their own money that had been put up as part of a deposit contract. Stitzer et al. (1977) that demonstrated that clinic privileges could be used to reinforce behavior change among opioid-dependent patients enrolled in methadone

therapy. Additionally, in one of the first demonstrations of monetary-based reinforcement for SUDs, Stitzer and Bigelow (1982) successfully manipulated rates of cigarette smoking by reinforcing objective demonstrations of reduced smoking with money.

During the 1980s and early 1990s a U.S. cocaine epidemic would shape the future of incentives research. By the mid-1980s a conservative estimate suggested that as many as 8 million Americans used cocaine regularly and that up to 8 % of users had developed serious cocaine dependence (Cregler and Mark 1986). However, that number rose alarmingly throughout the 1980's as crack cocaine, a pernicious formulation of smokeable cocaine, came onto the scene (Substance Abuse and Mental Health Services Administration (SAMHSA) 1988, 1989). By the mid 1980s, the use of crack cocaine had replaced heroin use as the main illicit drug problem in the United States with an estimated 1.5–1.75 million new users of cocaine appearing each year from 1980–1983 (Gfroerer and Brodsky 1992).

Not surprisingly, this cocaine epidemic created a tremendous need for effective treatments. Unfortunately, virtually all of the pharmacological and psychological approaches that were being investigated in the rush to find efficacious treatments were failing miserably. It was in that context that a series of controlled trails demonstrating that incentive-based treatment was effective in treating cocaine dependence garnered considerable notice (see Higgins et al. 2004a for a review). This effective treatment involved a model wherein outpatients earned vouchers, exchangeable for retail items in the community, contingent upon objective evidence of abstinence from recent cocaine use. This intervention was first introduced with an intensive form of counseling called the community reinforcement approach (CRA). This voucher-based incentives plus CRA approach was markedly more successful than usual care (Higgins et al. 1991, 1993; Fig. 9.1). Patients randomized to

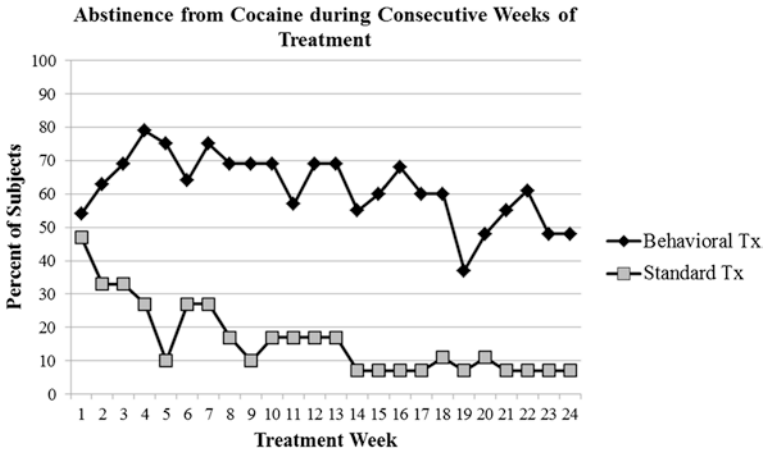

Fig. 9.1 Abstinence from cocaine among cocaine-dependent outpatients given behavioral treatment or standard drug abuse counseling. Reprinted with permission from Higgins et al. (1993)

the incentives plus CRA intervention achieved 5-fold better treatment attendance and 5- to 8-fold increases in cocaine abstinence at weeks 8 and 16 of 24-week trials compared to the usual care comparison condition. Later randomized controlled trials (Higgins et al. 1994; Higgins et al. 2000, 2003) experimentally demonstrated that the incentives portion of the intervention was the major, although by no means the only, contributor to the positive outcomes achieved with this incentive + CRA treatment approach. Subsequent trials demonstrated the efficacy of the model with diverse populations of cocaine dependent outpatients, including those residing in large inner city areas and minority populations that were especially hard-hit by the cocaine epidemic (e.g., Silverman et al. 1996).

The effectiveness of the incentives approach, where so many interventions had failed, plus the ease of adapting this treatment for use with other SUDs, and eventually other health-related behaviors, led to a surge of interest in developing more incentive-based interventions. One population that was also lacking an effective intervention was women who engaged in cigarette smoking during pregnancy. Smoking during pregnancy is the leading preventable cause of poor pregnancy outcomes in the U.S. and other industrialized countries, causing serious immediate and longer-term adverse effects for mothers and offspring (Cnattingius 2004). Counseling here too was having only small effects in this population (e.g., Solomon et al. 1996; Secker-Walker et al. 1998). In a series of controlled clinical trials, voucher-based incentives were shown to produce several-fold increases in smoking abstinence and improvements in birth outcomes (Heil et al. 2008; 2004b, 2010; see Higgins et al. 2012b for a review). Similar to the cocaine trials, incentives were found to be much more effective than usual care with a 4-fold increase in end of pregnancy abstinence levels in the treatment condition as compared to controls and improvements in birth weight that were proportional to the abstinence differences (Figs. 9.2 and 9.3).

There is a large body of positive evidence supporting the efficacy of incentives in the treatment of SUDs. A meta-analysis involving 30 controlled studies on incentive-based interventions demonstrated significantly improved rates of drug abstinence and treatment compliance compared to controls (Lussier et al. 2006). In another meta-analysis on interventions for smoking cessation during pregnancy, it was reported that commonly used behavioral and pharmacological interventions only resulted, on average, in a 6 % increase above control interventions in late-pregnancy point-prevalence abstinence rates whereas incentives-based interventions produced a 24 % improvement (Lumley et al. 2009).

Incentive-based interventions also have been extended into large work settings. In one example, over 800 employees of a multinational company based in the U.S. were randomly assigned to either receive financial incentives of various degrees and information about smoking-cessation programs or just information about the programs alone (Volpp et al. 2009). The financial incentives included $100 for completion of a program, $250 for smoking cessation within 6 months of program completion, and $400 for an additional 6 months of smoking abstinence after the initial cessation effort, all biochemically verified. The incentive group had significantly higher rates of enrollment in a cessation program, program completion, and cessation.

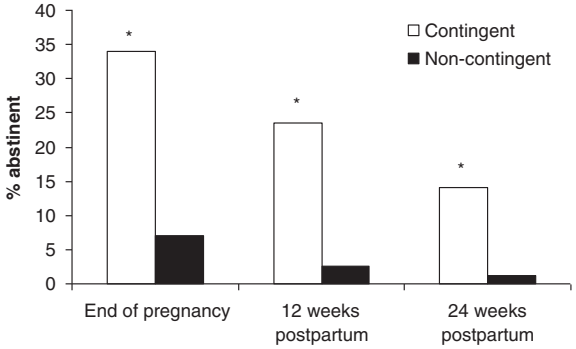

Fig. 9.2 Seven-day point-prevalence abstinence at the end-of-pregnancy, 12-, and 24-week postpartum assessments in the contingent (n = 85) and non-contingent (n = 81) treatment conditions. Treatment conditions are the same as described in Fig. 9.1. * indicates a significant difference between conditions (p = 0.003 or below across the three assessments). Reprinted with permission from Higgins et al. 2012

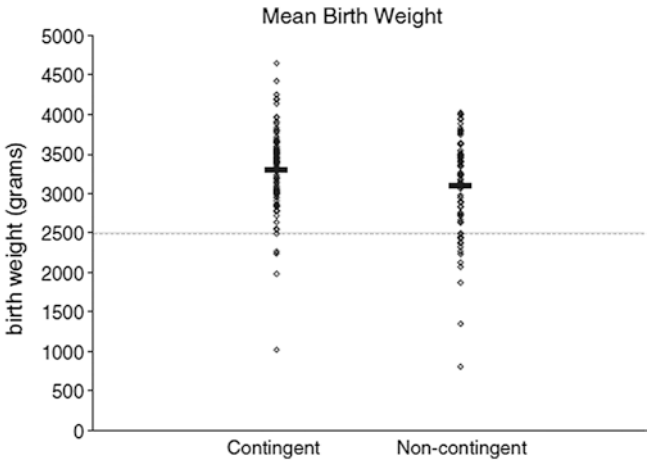

Fig. 9.3 Birth weights of infants born to mothers treated in the contingent (*left* column, n = 85) and non-contingent (*right* column, n = 81) treatment conditions. Each symbol represents an individual infant's birth weight and the *solid line* in each column represents the least square mean weight for that condition. The *dashed line* demarcates the 2,500 g cutoff for low birth weight. *Mean birth weight* differed significantly between treatment conditions (P = 0.03) as did the percent of low birth weight deliveries (P = 0.02). Reprinted with permission from Higgins et al. (2012)

However, when using incentives on a larger scale, programs must be designed carefully; with a loss of experimental control can come a loss in effectiveness. Objective verification of behavioral goals is key; deception may play a large role in interventions where objective monitoring is not used. One example is the

Quit and Win contests (Lando et al. 1994). These interventions attempt to target smoking cessation in whole communities while controlling costs by providing, as incentives, chances to win prizes donated by the community. However, a review of Quit and Win studies indicated that while the protocol appears promising, the number and quality of scientific studies examining these protocols is low and many of the studies that have been reported did not biochemically confirm abstinence, potentially allowing for a high level of deception (Cahill and Perera 2008).

Recent Developments/New Applications

Physical Inactivity/Weight Loss

In addition to SUDs, weight loss is another area where incentives research has a relatively long history, spanning over 50 years (e.g., Ferster et al. 1962). Incentive-based approaches in this area have varied over time. Most recently behavioral economic theory has come to be more prominent, mostly in terms of the rationale for using incentives, but also to a limited extent in the scheduling of incentive delivery (reviewed in Jeffery 2012). The behavioral economic viewpoint emphasizes the biases in decision making that were discussed above, especially the bias for the present. Present bias is a tendency to overweigh immediate gains and losses (Bickel and Marsch 2001). Individuals who suffer from health-related behavior problems seem especially prone to these biases (Cutler and Lleras-Muney 2010; Higgins and Chilcoat 2009; Kumanyika 2012). For example, a relatively large body of evidence demonstrates that individuals with SUDs discount the value of delayed rewards more than controls without SUDs (e.g., Bickel and Marsch 2001). The use of incentives leverages these vulnerabilities by providing short-term rewards over the course of developing long-term healthy behavior patterns. With the goal of leveraging this and other biases in decision-making, incentives for weight loss have been distributed in a variety of ways. Participants might be paid directly for weight loss, have money returned that they had deposited upfront, or be entered in "lotteries" for weight loss (reviewed in Jeffery 2012). All three approaches are successful to some extent over the short-term, but unfortunately in most cases weight is regained once treatment has ended. As such, development of effective weight loss maintenance contingencies is critical. In one study on this topic, data from two weight-loss trials (John et al. 2011; Volpp et al. 2008) were reanalyzed to more closely examine the effects of lottery versus deposit contract interventions and to see if any demographic variables were correlated with treatment success (John et al. 2012). No effect of race, education, income or marital status on intervention effectiveness was reported, arguing that these interventions have broad applicability. However, those with above average incomes were reported to respond more to deposit contracts while those of below average income appeared to respond better to lottery interventions.

Managing Chronic Disease: Medication Adherence

Another important area of health research where incentives have the potential to make a substantive contribution is medication adherence. The World Health Organization (Sabaté 2003) estimates that only 50 % of patients with chronic health problems within developed countries adhere to (i.e., take ≥80 % of) their medication regimens. A recent literature review on the utility of monetary incentives for improving rates of medication adherence was reported by DeFulio and Silverman (2012). The studies reviewed largely focused on improving adherence to medications used to treat SUDs and related diseases (naltrexone, disulfiram, nicotine gum, antiretroviral therapy), but also included adherence to tuberculosis treatment, hypertension medications, and warfarin therapy. The area was surprisingly undeveloped. For example, no single study reviewed included both experimental controls and a large sample size. However, the results of many of the smaller studies were nevertheless promising. For example, Rosen et al. (2007) examined the use of incentives for increasing adherence to antiretroviral medications for HIV infection. Participants who received chances for lottery-based prizes for adherence were significantly more likely to adhere to their medication regime and had lower viral loads than controls. Overall, the authors concluded that moderate value incentives ($100/month or greater) were able to substantially increase medication adherence (DeFulio and Silverman 2012). Considering the considerable economic costs associated with non-adherence in terms of increased hospitalizations, lost productivity, etc., incentive-based interventions targeted at improving adherence could prove to be highly cost-effective, although this remains to be demonstrated empirically.

Pay-for-Performance Interventions

While incentives have most typically been applied to promote behavior change among patients, there is also growing interest in their use to promote behavior change among health care providers (Scott et al. 2011). Pay-for-performance (P4P), where physicians or other healthcare providers are rewarded for improving particular aspects of healthcare delivery, is being considered broadly as a strategy for improving outcomes in patients with chronic disease (e.g., Peterson et al. 2006; Dudley et al. 2004). Indeed, recent legislation in the United States has mandated the evaluation of P4P incentives in governmentally funded programs that care mostly for lower SES or minority patients (e.g., Medicaid, Tricare, Veterans Health Administration; H.R. 3590 2009; Exec. Order No. 13410 2006), which, as might be expected, has increased interest in evaluating the P4P model. One such study, for example, examined outcomes in the Hudson Health Plan's P4P program aimed at improving the process of diabetes care, outcomes, and related healthcare utilization in New York state from 2003 to 2007 (Chien et al. 2012). Diabetes

care processes (e.g., HbA1c, lipid, dilated eye exam rates) and outcomes (e.g., LDL-C < 100 mg/dL) did not significantly improve following implementation of P4P. Of additional concern, younger adults and those with more co-morbidities received less recommended care and were more likely to have a diabetes-related emergency department visit or hospitalization, indicating that more or different outreach and management may be warranted. While there is growing interest in the potential utility of P4P strategies in improving outcomes in the management of chronic disease, empirical evaluations are in the very early stages and the incentive schemes have often been quite rudimentary. With incentives for physicians, for example, often amounting to less than 10 % of their income it is not surprising that health outcomes are not always positive (Rowe 2006). Nevertheless, this is an area where there is tremendous interest and potential for incentives to make a positive contribution to improving outcomes and reducing costs.

Global Health

An area where monetary incentives are being examined on a large scale and with promising results is in international efforts to combat chronic poverty—referred to as conditional cash transfer (CCT) interventions. CCT interventions are implemented in low- and middle-income countries where impoverished mothers receive cash payments conditional on having their infants inoculated, attending well-baby check-ups, enrolling and keeping the children in school, and in some cases being tested for HIV infection or sexually transmitted diseases (Ranganathan and Lagarde 2012). CCT programs are often effective at improving use of health services and health outcomes in these populations. In one example in rural Mexico, for example, a CCT program led to a 17 % decline in rural infant mortality. These programs are promising and uniquely large in scale, although the multi-component nature of the interventions can complicate interpretation of outcomes (Ranganathan and Lagarde 2012).

Another area of global health where the use of incentives has had promising effects is in the area of family planning (see Heil et al. 2012 for a review). With the ever increasing (and accelerating) world population growth, driven mainly by decreases in child mortality due to better treatments for infectious disease, family planning has become an area of increasing concern. Living in a world of finite resources, controlling the population seems a necessary step and encouraging voluntary family planning as a means to that end would potentially have a huge effect. Various countries have long held this opinion and in fact family planning is another area with a long history of the use of incentives, with the earliest published studies dating back to the 1950s (see review in Elder and Estey 1992). Family planning interventions have taken many forms from offering incentives for sterilization to providing bank accounts and retirement funds for those who have a limited number of children. Of the handful of studies that report some kind of control condition (see Heil et al. 2012 for a review), seven out of eight report positive family planning outcomes (e.g., use of contraception, increased birth spacing, fewer

children per family). In one example, women in Accra, Ghana in West Africa were given either referral slips to a family planning clinic or a referral slip and a coupon that could be redeemed for powdered milk at the clinic. The number of women accepting family planning methods increased 2-fold with the incentives and 3-fold when the referring field workers were also offered incentives (Fig. 9.4; Perkin 1970). Unfortunately, the use of incentives in family planning can be controversial (as in other areas as well, see later in this chapter), the pay-for-sterilizations in India were seen especially to be coercive. However, incentives can be used in family planning in a positive manner. Incentives can be provided for birth spacing, which promotes better health in the mother and child, or incentives can be given for the proper use of contraception in women who do not want additional children (Feldman et al. 2009). The fact that there exists a preponderance of unintended pregnancies each year argues for a place for incentives in family planning.

Public Perception/Ethics

The use of incentives to promote health can be a controversial subject. Despite considerable empirical evidence supporting its efficacy, the public has often reacted negatively to the concept of "paying" people to behave in a healthy manner (e.g., Long et al. 2008; Parke et al. 2011; Priebe et al. 2010). Part of this negativity may be the perception that one should not have to incentivize someone to do what they should be doing anyway. However, this simplistic view of motivated

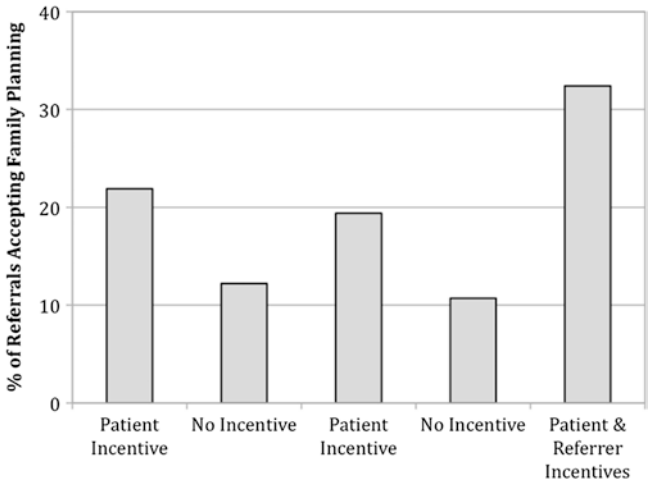

Fig. 9.4 Percentage of referrals accepting family planning when participants were offered a referral slip plus a tinned milk incentive for attending a family planning session (weeks 1 and 3), a referral slip alone (weeks 2 and 4), or a referral slip and tinned milk incentives for both participants and referrers (week 5). The study was conducted in Accra, Ghana, in West Africa in the late 1960s. Reprinted with permission from Heil et al. (2012)

behavior overlooks the fact that nobody sets out to become addicted to cigarette smoking or other drugs, to be obese, etc., and that many people require at least some help in successfully changing the longstanding behavior patterns that lead to such problems. These and other concerns regarding incentives and health have led researchers in this area to explore the ethics of such practices.

As mentioned above, the crux of ethical arguments against using incentives to promote healthy behavior is that people should not need to be paid to engage in behavior change and that doing so might undermine longer-term motivation to be healthy (Halpern et al. 2009). From a classical economic perspective makes some sense; that is, man is assumed to be rational and sub-optimal behavior must be due to a lack of information (Loewenstein 2000; Loewenstein et al. 2008). However, we know from the behavioral biases mentioned previously (e.g., present bias, etc.) that this perspective is oversimplified and largely inaccurate, at least with regard to health-related decision making. Despite abundant information about the health risks associated with smoking, obesity, etc., people continue to use drugs, overeat, shun exercise and suffer from the diseases that result from these unhealthy practices (Schroeder 2007). And, of course, the costs of those diseases and related outcomes are almost always shared by others, either by others under the same insurance plan or nationally in the cases of costs borne by Medicaid/Medicare. As incentives have been found to be effective for treating a large range of behavioral issues from smoking (e.g. Higgins et al. 2012a, b) to obesity (Volpp et al. 2008), one might reasonably reframe the question to ask if it is actually ethical to not use incentives (i.e., to withhold an effective treatment). While some object that incentives infringe on free will, disproportionately target low-SES populations, or subvert intrinsic motivation to change (Halpern et al. 2009), it is important to underscore that incentives do not obviate choice; that is, individuals are free to pass on the incentives and continue in the unhealthy behavior pattern being targeted by the intervention. Regarding the SES matter, taxes on cigarettes (and now on sugary beverages) already disproportionately affect low-SES populations. In that regard, incentives if successful can represent a means of escaping from such targeting rather than promoting it. Lastly, with regard to the concerns about undermining intrinsic motivation, we know of no evidence to support that claim with regard to health-related behavior.

To gain greater understanding of the public acceptability of incentive-based interventions, researchers have begun to conduct systematic studies rather than relying on anecdotal accounts. A study by Park et al. (2012) provides an excellent example of this area of research. These investigators surveyed a representative sample of the Philadelphia public to examine if they perceived incentive-based interventions as less acceptable than other treatment methods using smoking cessation as an exemplar. Potential participants were approached at major Philadelphia transportation depots with the resulting sample population approximating the demographic profile of the greater Philadelphia area. Surprisingly, unlike the researchers' predictions, people were not significantly less accepting of an incentive treatment than a medication treatment for smoking cessation. These results were consistent with some (Long et al. 2008) although not all (Promberger et al. 2011) previous research. Other research suggests that details of the

effectiveness of the treatment as well as the target behavior may also be important variables (Promberger et al. 2012). In a survey conducted in the UK, individuals were more accepting of incentive-based treatments as the hypothetical effectiveness of such treatments increased. Also, paying people to lose weight was seen as more acceptable than paying someone to stop smoking. These findings are intriguing considering the health outcomes of both smoking and obesity will impact the cost of healthcare for everyone. Insensitivity of the public to this issue is also reflected in Park et al. (2012) research, where they found that only about 40 % of those surveyed would support treatments of any kind if those treatments would cost them even a small amount of money ($25/year) even when reminded of the high societal costs of continued smoking (>$2,000/year). Perhaps if the connection between the additional health costs of smoking and one's personal healthcare costs could be made more explicit, public opinion of publically funded smoking treatments, independent of modality, would be higher.

While researchers have confronted the ethical and public perception implications of the use of incentives for treatment in patient populations, as incentives move into the workplace setting and the context of general wellness programs other ethical issues are arising. Many of these concerns are reviewed in Schmidt et al. (2012). One issue is the ethics of what exactly should be incentivized. Is it ethical to reward people based on outcomes, which not everyone may be able to obtain, or should we only incentivize effort, under the assumption that everyone can at least try? Even choosing to incentivize effort does not abolish the fairness issue. Consider, for example, a person who is given the task of reducing their cholesterol to normal levels. The person could attempt to eat a more healthy diet; however, if they live in a "food desert" such foods may not be readily available. They may attempt to increase their physical activity, but if they are a single mom working two jobs they may have very little time for such an endeavor. Incentive programs, especially those run by employers and insurance companies will need to consider such questions when developing incentive schemes. Programs could be designed to allow for all participants to have a roughly equal chance of earning the incentives. However, effectiveness must be considered carefully when weighing "fairness". An incentive program that rewards effort but is ineffective in producing the desired outcome is not preferable to the program that rewards outcomes, which may be selectively effective, but does engender success in at least some participants.

Conclusion

Thus far the evidence points to monetary incentive programs being an effective treatment for a variety of SUDs as well as a promising new approach to treating a plethora of other health-related behavior problems and associated disorders. As we move forward, the challenge is shifting in some areas (such as SUDs) to one of how to disseminate these treatments more widely. One of the major concerns/limitations associated with the use of incentive interventions is the cost. Although

on a larger scale, the short-term costs of incentives often appear to be outweighed by longer-term health savings (e.g., Silverman et al. 2008), finding the initial funds for these treatments can be challenging. Given the disconnect between health costs now and health costs later in the multi-payer insurance system of the U.S., it is sometimes in no one's best financial interest to help individuals overcome unhealthy behavior patterns in the near term. In a single-payer system where one entity is responsible for the health costs of an individual from cradle to grave, perhaps the idea of using public money to help motivate individual behavior change may be more palatable. Even in the messy, multi-stake-holder U.S. healthcare system, though, the idea of using incentives for healthy behavior change is gaining acceptance. With the introduction of the U.S. Patient Protection and Affordable Care Act, for example, private employers are now allowed to use up to 30 % of the costs of an employee's health insurance coverage as incentives to promote wellness (Patient Protection and Affordable Care Act of 2010). This Act also mandates that $100 million of Medicaid funds be allocated to 10 states to evaluate the use of incentives to increase participation in disease prevention programs (see http://www.CMS.gov., 2012).

Of course, governments and healthcare systems are not the only players in the realm of incentives. A recent estimate states that one-third of all large employers in the U.S. are using financial incentives in their employee wellness programs (Mercer: Consulting, Outsourcing, Investments 2011) and the number continues to grow. Entire companies are emerging to manage these new incentive programs, Chip Rewards (chiprewards.com) is just one example. Individuals can also access widely available tools to use incentives to motivate personal behavior change. One example of this emerging trend is the website stickk.com where individuals can publically commit to behavioral goals backed by their own money. To motivate the individual to change, if those goals are not met, their money is donated to a cause that the individual does not particularly like (e.g., the opposing political party). The emergence of these companies, aimed at both workplaces and individuals, speaks to the increasing acceptance of incentives as a method for motivating behavior change.

Future Directions

With the past successes of incentives as well as the number of health-related behavior patterns that could use improving, the possibilities for future application are vast. Behavior patterns related to the management of chronic conditions (e.g., diabetes, hypertension) as well as for relatively acute circumstances (e.g., encouraging smoking cessation post-surgery to increase wound healing) are all potential areas for future exploration in this field. Potential secondary prevention applications are also numerous. Cardiac rehabilitation (CR) provides an excellent example (Ades and Gaalema 2012). CR, a structured exercise program, has a proven record of decreasing morbidity and mortality in patients who have experienced

recent cardiac events. However, only 19–55 % of eligible patients participate in CR (Suaya et al. 2007; Centers for Disease Control 2003; Witt et al. 2004). These numbers are even more break in low-SES populations. Incentives have proven effective in low-SES populations and as such CR seems a promising area duction of incentive-based treatments.

We fully anticipate that this field will continue to grow. Even in areas such as SUDs, where incentives have been most extensively studied, researchers continue to refine techniques and explore sources of individual differences in treatment response. We anticipate the Patient Protection and Affordable Health Care Act will drive further innovation around incentives as part of efforts to curtail the growth in health care costs in the private and public sector (Patient Protection and Affordable Care Act of 2010). As an example of growth in this direction in the public sector, legislation is being considered by the U.S. Congress to incentivize participation in smoking cessation and other health prevention activities among Medicare patients (H.R. 6232: Medicare Better Health Rewards Program Act of 2012; see http://www.govtrack.us/congress/bills/112/hr6232/text). Additionally, we anticipate continued growth in the use of CCT programs in developing and middle income countries and perhaps in response to the growth of poverty in developed countries as well (Yoshikawa et al. 2012).

Highlights

- This chapter provides a detailed overview of research on the use of monetary incentives to produce health-related behavior change; these interventions leverage the same reward processes that underpin vulnerability to substance abuse, overeating, and other unhealthy behavior patterns to increase healthier choices.
- Incentives have been examined across a range of health problems, including SUDs, physical inactivity/weight loss, and medication adherence.
- These programs have been investigated in studies ranging from initial proof of concept investigations examining drug use as a modifiable behavior to large-scale community interventions such as Conditional Cash Transfers, used to combat chronic poverty in low and middle income countries.
- Unhealthy personal behaviors account for approximately 40 % of premature deaths in the United States each year, opening the door for potential wide-scale implementations of incentive-based interventions to improve U.S. population health.

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Part IV
Social Connections, Socioeconomic Status and Stress

Chapter 10
Social Relationships and Public Health: A Social Neuroscience Perspective Focusing on the Opioid System

Baldwin M. Way

Whether it be dinner with a spouse or working on a proposal with a co-worker, our daily lives are filled with social interactions. Over the last 40 years, a robust body of evidence has emerged indicating that the frequency and quality of these interactions impact not only psychological well-being, but also physical health. A recent meta-analysis of studies examining the effects of social relationships on mortality compellingly demonstrates the robustness of this effect. Based primarily on prospective studies, impoverished social relationships have an effect on mortality comparable in magnitude to that of cigarette smoking. This effect is greater than that of regular exercise, obesity, and even pharmacological treatment for hypertension (Holt-Lunstad et al. 2010). Thus, it appears that a doctor's best health advice to a patient is: "Go see a friend."

With such profound influences on health, it is imperative to understand the mechanisms by which social relationships impact health. If these pathways are better understood, perhaps environments or interventions that foster more positive social interactions can be created and thereby improve public health. Although identifying these mechanisms has been a goal since the first studies establishing a link between social relationships and health in the 1970's, progress on this front has been slow (Thoits 2011). Much of this research has focused on identifying the psychological mechanisms for this effect and it is proposed here that supplementing this research with neuroscientific, and particularly neurochemical data, may foster advances in understanding of the mechanisms by which social interactions affect health. To provide a background for this approach, the proposed psychological mechanisms for social influences on health will be discussed in the next section before turning to hypotheses concerning the neurochemical mechanisms underlying social relationships.

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Psychological Mechanisms for Social Effects on Health

The web of interactions each human has with others is obviously intricately complex. Nevertheless, these interactions have generally been reduced to several gross measures that are commonly used in health research. The structure of social interactions is often measured by the degree of social integration, which refers to the social ties that an individual has with others whether they be members of primary groups such as the family or secondary groups such as someone who attends the same church. Often the frequency and regularity of these interactions is also recorded. Another common measure is perceived social support, which refers to the degree to which one feels that one has readily available sources of emotional, informational, and instrumental support (House et al. 1985). Received support refers to the actual exchange of these resources (Dunkel-Schetter and Bennett 1990).

These particular measures are delineated here, because they are thought to effect health via different mechanisms. For example, perceived social support has been argued to be particularly important in the face of stress, serving as a buffer against the adverse consequences of stress (Cohen and Wills 1985). Social integration, on the other hand, has been argued to be less important in the face of stress, but rather have primarily main effects on health (Cohen 2004). Studies of received support have revealed inconsistent effects on health, with many studies actually reporting links between received social support and *higher* mortality (e.g. (Krause 1997). Hypotheses to explain these counterintuitive effects of received support are beyond the scope of this chapter (for a further discussion, see (Uchino 2009), but suffice it to say that there is much still to be learned about the mechanisms by which social support operates. For the sake of discussion here, main effects of social interactions, encompassing both social integration and perceived social support, will be focused upon (Lakey and Orehek 2011).

Multiple psychological pathways for social support and social integration have been proposed. For example, higher social support has been linked to greater self-esteem (Symister and Friend 2003), greater positive affect (Diener and Seligman 2002), and lower depression (Russell and Cutrona 1991). It would seem natural that these would be viable mediating pathways by which social interactions influence health. However, the mediating role for such psychological processes upon physical health outcomes has been exceedingly difficult to document for either measures of social support or social integration (Thoits 2011). This lack of reliable psychological mediators is not limited to epidemiological studies, but is also seen in laboratory stress studies. Studies that manipulate social support prior to or during a stressor often show robust effects of the manipulation on reducing physiological measures of stress (e.g., cardiovascular reactivity), but rarely document mediating effects of self-reported affect or stress. Uchino et al. 2012 succinctly summarize both epidemiological and laboratory studies of social support by stating “In general, the available recent literature provides no evidence that the influence of perceived or received social support on cardiovascular, neuroendocrine, and/or immunity is statistically mediated by anxiety, life stress, subjective stress, or depression.” (Uchino et al. 2012, p. 951).

This is a rather disheartening conclusion and forces a return to the drawing board, and in particular the aforementioned epidemiological studies as they may provide a clue to the potential mechanisms responsible for this relationship. Although there are few measures in health psychology and social neuroscience that can be as reliably measured as mortality, there are many different routes to this end point. A natural question is whether or not social relationships contribute equally to these outcomes or whether there are particular diseases that are most influenced by social relationships and are the main contributors to the demonstrated effects of social relationships on mortality. Although the number of studies upon which to draw is smaller, there do not appear to be major differences across diseases. In other words, having richer social relationships appears to reduce the risk of dying from diseases as diverse as cardiovascular disease (Barth et al. 2010), infectious disease (Lee and Rotheram-Borus 2001), and cancer (Pinquart and Duberstein 2010). Because these diseases have very different etiologies, it suggests that physiological systems that affect multiple biological targets are likely to be involved. Examples of such systems would be the autonomic nervous system, hypothalamic–pituitary–adrenal (HPA) stress axis, and the immune system. The question then becomes, do social interactions impact these pathways directly? In other words, do social interactions directly trigger activation or deactivation of these systems by pathways that are automatic or not fully accessible to the explicit recollection that forms the foundations for the self-reported experiences that are recorded with psychological measures?

Social Interactions and Health-Relevant Peripheral Physiological Pathways

The clearest data for social interaction effects on peripheral physiology comes from the studies of ambulatory blood pressure, which is a good predictor of mortality as well as hypertension and other adverse cardiovascular outcomes (Boggia et al. 2011). In an experience sampling study assessing social interactions of adults, interacting with one's partner, relative to strangers or being alone, was associated with reduced systolic (SBP) and diastolic blood pressure (Gump et al. 2001). Not surprisingly, measures of arousal, intimacy, and emotional support were significantly higher when interacting with one's partner. However, these did not mediate the effects of the social situation upon blood pressure. Similar results were seen in a study of healthy adults (Holt-Lunstad et al. 2003), where being in the presence of family members or a spouse was associated with lower systolic and diastolic blood pressure than being around nonfamily members. Again, even though these social relationships were associated with differences in affect, intimacy, and disclosure these psychological variables did not mediate the effect. In the work environment, traffic agents interacting with a coworker had lower SBP and lower negative affect than when interacting with a stranger (Brondolo et al. 1999). However, affective state did not mediate the effects of the social situation on blood pressure. Thus,

being with close to others seems to have a positive effect on cardiovascular function by mechanisms that may not necessarily be accessible to conscious awareness.

With respect to cortisol as a measure of HPA axis output, there is evidence for social influences on cortisol reactivity throughout the lifespan. For example, in infants, sensitive parenting can blunt the cortisol response to separation stress (Gunnar and Donzella 2002). This has also been seen in adolescents where an experience sampling study showed that when adolescents were alone, they had 14 % higher cortisol levels than when they were with others, controlling for time of day effects (Adam 2006). Just like with the previously described cardiovascular studies, the effect of social interactions on this physiological marker controlled for self-reported emotional experience, which indicates that feeling distressed is not necessary for activation of physiological systems with health relevance. Similar results were found in an experience sampling study with college students, where solitude was associated with higher cortisol (Matias et al. 2011). Again, this effect was not mediated by negative affect or positive affect. In adults, there is evidence that social networks (Lai et al. 2012), social support (Heaney et al. 2010), and loneliness (Adam et al. 2006) can affect diurnal patterns in cortisol activity. At the same time, there is also evidence that negative affective states are associated with momentary cortisol levels as well (e.g., Smyth et al. 1998). However, there has not been much evidence for a mediating role of affective state between social interactions and HPA axis activity. Taken together, these studies suggest that social interactions can impact HPA axis activity, but that it is not necessary that these social effects impact psychological state.

In addition to these studies in humans, there is corroborative evidence from nonhuman primates where social behavior can be more accurately quantified due to the ability to systematically observe their social interactions in a way that is not possible in human studies. The nonhuman primate model is highly applicable to social influences on health, as social bonds are related to longevity in nonhuman primates as well. For example, female baboons that have greater social integration, as measured by the time spent in proximity with others and grooming others, live longer. The effects of stable relationships of this type on longevity are independent from and stronger than the effects of dominance status (Silk et al. 2010).

Although the link between HPA axis activity and longevity has not been directly made, it is a likely candidate for being a contributing mediator of such effects. Across nonhuman primates, species socially organized such that subordinates have good social support have lower cortisol levels than those species where subordinates do not have access to such support (Abbott et al. 2003). In wild male yellow baboons (Sapolsky et al. 1997) as well as wild male olive baboons (Ray and Sapolsky 1992), males who spend more time grooming and in the proximity of others have lower levels of cortisol. Similarly, in captive female rhesus monkeys, animals that are higher on sociability have lower cortisol levels throughout most of the year (Gust et al. 1993). Interestingly, more recent work using social network analysis in both female rhesus monkeys (Brent et al. 2011) as well as female baboons (Wittig et al. 2008) in the wild shows that it is particularly focused social relationships that tend to be associated with lower glucocorticoid levels (as measured in fecal matter), which are presumed to reflect HPA axis output. In other words, having

a few reliable relationships appears to reduce HPA axis activity more than having a broader social network that has less reliability. This will be an important issue to address in future research in human social epidemiology studies.

One system highly influenced by cortisol is the immune system. This system has a better documented impact on health outcomes than the HPA axis, as it directly affects disease processes such as atherosclerosis or viral infection. Just like in the HPA axis, there are robust effects of sociality on the immune system. However, whether the effects of social interactions upon immune parameters are mediated by HPA axis activation or not is less clear and likely to vary depending on the measure and the experience of the individual or animal. In captive long-tailed macaques, natural killer cell activity is highest among those who are more social (Kaplan et al. 1991). In rhesus macaques, differences in levels of social interaction were associated with the degree of sympathetic nervous system fibers innervating the lymph nodes (Sloan et al. 2008), indicating that differences in sociability are linked to structural differences in the sympathetic nervous system. Although correlational, these data are suggestive that it is the greater stress associated with lower levels of sociality that lead to these structural changes, as stress can lead to increases in sympathetic innervation (Sloan et al. 2007). These low sociable animals also had poorer antibody response to vaccination, which would be consistent with placing them at greater risk for viral infection.

Overall, these nonhuman primate studies indicate that frequent social interactions with other members of the species reduce activity in peripheral physiological systems relevant to health. Although the subjective correlates of these effects are obviously open to interpretation, they provide compelling support for a direct effects pathway by which social interactions can influence potential downstream physiological processes and thereby contribute to disease progression and onset.

If we return to the central question concerning the mechanisms by which social interactions affect mortality, it seems that social interactions trigger peripheral physiological pathways that can affect disease. However, this still begs the question as to how one category of stimulus, social interactions, trigger these multiple pathways. Do social interactions stimulate each of these peripheral physiological systems separately? Or, do different components of social interactions stimulate a particular system? Do social interactions stimulate one upstream system that then triggers each of these peripheral physiological systems in common? The working hypothesis here is that social relationships act on a common pathway in the brain to trigger these downstream pathways. Thus, social interactions activate a minimal number of systems in the brain which then trigger these multiple downstream pathways. Admittedly, this is a bold claim. After all, if a drug company salesman advertised that he had a drug that could help reduce risk of all-cause mortality, he would naturally be ridiculed as a peddler of snake-oil, because a drug should only affect one specific biochemical pathway involved in a particular disease. Yet, social relationships seem to be a “drug” that have effects across a variety of diseases. How they might have such a common effect is the subject of the next section.

Neural and Neurochemical Processing of Social Interactions

Where in the brain are social interactions processed? There are many areas, but one of particular relevance here are the reward pathways. Converging evidence from both pharmacological and neuroimaging studies suggests that there is tremendous overlap between the processing of social stimlui that are rewarding and general rewarding stimuli such as money (Knutson et al. 2000) or food (McClure et al. 2007). For example, anticipation of social approval in the form of friendly faces (Spreckelmeyer et al. 2009) activates overlapping ventral striatal circuits with that of the anticipation of money. Similar overlapping activation was seen when acquiring a favorable social reputation or acquiring financial reward (Izuma et al. 2008). Although there is tremendous overlap between social and nonsocial rewards, this is not to say the two are identical, as particularly in the consummatory phase of reward there is greater delineation between them (Rademacher et al. 2010).

This neural activity in the reward centers of the brain while processing social stimuli is of relevance for health measures, most notably pain. Viewing pictures of a romantic partner reduces the aversiveness of experimental pain stimuli, relative to viewing pictures of a stranger (Eisenberger et al. 2011; Master et al. 2009; Younger et al. 2010). The activity in the ventral striatum (Younger et al. 2010) and the VMPFC (Eisenberger et al. 2011) correlates with the degree of pain reduction, suggesting that the greater degree to which seeing a romantic partner activates these areas, the greater reduction in pain.

Although these neuroimaging studies do not identify the neurochemical system involved, one system that could be involved in both social reward as well as social analgesia is the opioid system. In particular, the μ-opioid receptor is probably best known for being the site of action for both morphine, the prototypical painkiller, and heroin, the prototypical euphorogenic drug of abuse. Both the rewarding and pain suppressing effects of stimulation of the μ-opioid receptor are likely to be of relevance for understanding the mechanisms by which social interactions impact health outcomes. In the normal individual, the μ-opioid receptor is acted upon by several opioid neurotransmitters, most particularly β -endorphin and the enkephalins (S. H. Snyder and Pasternak 2003), which will be referred to here as the endogenous opioids.

This notion of opioid involvement in social bonds was first recognized by Jaak Panksepp in the 1970's and has received recent theoretical elaboration. For example, Depue and Morrone-Strupinksy (2005) relied heavily upon the opioid system in their neurobehavioral theory of affiliative bonding as did Machin and Dunbar (Machin and Dunbar 2011) in their Brain Opioid Theory of Social Attachment (BOTSA). The basic underlying premise of these theories is that social interactions trigger opioid release, which then acts on the μ-opioid receptor to form and maintain social bonds.

A social bond is loosely defined here as an enduring, interdependent social relationship that is characterized by a felt sense of belonging as well as a set of behaviors indicative of closeness such as frequency of interaction, degree of

influence on each other, and willingness to engage in altruistic behaviors for the well-being of the other (Aron et al. 1992; Berscheid et al. 1989). Although these certainly apply to romantic relationships, this definition also includes familial relationships and friendships. Even more broadly, there is no reason to postulate that this type of bond does not extend to pets, which can reduce stress (Allen et al. 2002). Furthermore, parasocial relationships, such as those encountered in television shows or fictional works can also provide an experience of belonging (Derrick et al. 2009), serving as social surrogates much like cloth surrogates in Harlow's (Harlow 1958) classic studies on infant monkeys separated from their mothers.

There is evidence indicating that opioids are involved in both the formation of social bonds as well as their maintenance. This has been most clearly established in the bond between the mother and the infant. In sheep, blockade of opioid signaling in the lamb within the first few hours after birth prevents it from forming a preference for the mother (Shayit et al. 2003). This has been corroborated via genetic means as well. μ-opioid receptor knockout mice have deficits in selective approach of their mothers, indicating that they have not formed a bond with them (Moles et al. 2004). This early formation of the bond may be important for the proper formation of later social relationships, as mice given naltrexone during development to block the formation of their bond with the mother seek out less social interaction and find it less rewarding when they are adolescents (Cinque et al. 2012). This suggests that the early attachment bond is important for later relationships as well. In other words, the mechanisms underlying attachment to the mother extend to other relationships (Broad et al.2006). Consistent with this, in adult prairie voles which normally form a pair-bond after mating, antagonism of the μ-opioid receptor prevents the formation of this bond (Burkett et al. 2011).

Opioids may also be involved in the maintenance of social bonds between peers. In primates, grooming fosters social cohesion and elicits release of endogenous opioids (Keverne et al. 1989) and also reduces sympathetic activation (Aureli et al. 1999). Similarly in adolescent rodents, endogenous opioids are released during play (Vanderschuren et al. 1995). Unfortunately, there is minimal human data upon which to verify these findings, but based on the social changes in heroin addicts (Rosenbaum 1981), it would appear that the opioids operate similarly in humans. In such individuals, the drug substitutes for social bonds and they find maintaining their social relationships less rewarding.

Such observations of heroin addicts are what led Panksepp and colleagues (Panksepp et al. 1980) to form their initial hypothesis. In particular, he noted that the behavioral manifestations of social separation (e.g., romantic breakup) and heroin withdrawal were similar. Both share an increase in sleeplessness, irritability, the stress hormone cortisol, depressive feelings, and loss of appetite. This made him wonder if a fall in endogenous opioids were contributing to the behaviors associated with social separations such as the death of a loved one or a romantic breakup. To test this hypothesis, he and others administered low doses of morphine to infants of various species [monkeys: (Kalin et al. 1988); dogs: (Panksepp et al. 1978); guinea pigs: (Herman and Panksepp 1978); rats: (Carden et al. 1991); and chickens: (Warnick et al. 2005)] and found that it reduced the

behavioral manifestations of distress upon separation from the mother. This data suggests that the stimulation of the μ-opioid receptor by morphine is remedying a fall in endogenous opioid signaling due to removal of the mother.

A natural question is whether this occurs in humans, and of particular relevance to the topic here, does it extend beyond the maternal-infant bond to bonds between adults. Based on Positron Emission Tomography (PET) scanning of μ-opioid receptor mediated transmission in women, it appears that a decrease in social connection might be associated with reduced endogenous signaling at the μ-opioid receptor (Zubieta et al. 2003). When participants recalled the death of a loved one or the break-up of a romantic relationship, there was a decrease in endogenous opioid release. The technical challenges of this type of study though limit the interpretation as the participants need to recall this event for 30 min to obtain a reliable measure of μ-opioid mediated neurotransmission and naturally the narrow bore of the scanner precludes actual social interaction.

Further corroborative evidence comes from a study of genetic variation in the μ-opioid receptor gene (*OPRM1*). Within exon 1 of this gene, there is a polymorphism (A118G) that leads to reduced expression of the μ-opioid receptor (PET and mouse studies). An association study of the relationship between this polymorphism and social rejection, indicated that the *OPRM1* G allele is associated with greater self-reported dispositional concern and worry about social rejection (Way et al. 2009). These dispositional concerns over being excluded by others are also manifest in the neural response to an actual experience of social exclusion. Carriers of the G allele exhibited greater activity within the dACC and anterior insula when being excluded from an online ball-tossing game (Cyberball).

Although it is difficult to draw inferences concerning the efficacy of μ-opioid mediated signaling from genetic association studies like this, these data do suggest that the opioid system is involved in the response to separation from other individuals. Most importantly, the other individuals in this experiment were not attachment figures, so this study also suggests that the opioid system is involved in multiple types of relationships. It will be an important question for future research to identify the degree to which shifts in μ-opioid mediated neurotransmission are affected by different types of relationships. In sum, human studies corroborate animal studies and indicate that social separation leads to a decrease in opioid mediated neurotransmission.

Effects of Endogenous Opioids on Peripheral Physiology

In addition to instantiating social bonds at the neurochemical level, the opioids may also be critical mediators of peripheral pathways that can elicit the physiological effects that exacerbate disease. This is an important component to the notion that endogenous opioids might be involved in mediating the effects of social relationships upon health.

The effects of the central opioid system on peripheral physiology has been most clearly demonstrated for the HPA axis. The μ-opioid receptor is localized in the paraventricular nucleus of the hypothalamus (Zheng et al. 2005), which is the location of the Corticotrophin Releasing Hormone (CRH) cells that initiate the hypothalamic–pituitary–adrenal stress axis response that culminates in the release of cortisol into the bloodstream. Studies of the firing properties of cells in this region indicate that stimulation of the μ-opioid receptor has an inhibitory effect (Wuarin and Dudek 1996). This is consistent with studies showing that morphine administration inhibits cortisol release (Zis et al. 1984) and that withdrawal from morphine leads to robust cortisol release (Drolet et al. 2001)—a critical component of the aversiveness of withdrawal from this drug. Thus, based on the fall in levels of opioids seen when separated from a valuable social contact, it is reasonable to postulate this as a mechanism mediating the stress response seen with the loss of social support.

The effects of a fall in opioids are not limited to the HPA axis. There is also evidence that the loss in μ-opioid receptor stimulation can lead to large increases in sympathetic output and loss of parasympathetic tone, which can drive a pro-inflammatory state (Kienbaum et al. 2002). Thus, the opioid system is potentially a critical link in transducing the positive effects of social interactions into peripheral physiological effects.

Toward a Model of Opioid Involvement in Social Effects on Health

Based on the discussion, thus far, the working model is that social interactions increase the levels of neurotransmitters that signal through the μ-opioid receptor, which lead to better physiological regulation and health. Therefore, it would seem that the path forward for the field is to assess how different forms of social interactions impact μ-opioid mediated neurotransmission and subsequent peripheral physiological measures. This would go a long ways toward establishing the opioid system as a critical mediator of the effects of social interactions on health.

One could gain the impression from this review that psychological factors are irrelevant for understanding the mechanisms by which social interactions impact health. However, just because psychological processes do not appear to mediate the social effects on health does not mean they do not moderate them. In fact, assessment of neurochemical measures at the exclusion of psychological one's is unlikely to lead to significant advancements in understanding the mechanisms by which social influences affect health. Social stimuli are likely to differentially activate the opioid system as a function of multiple psychological variables such as family history and personality. Inattention to these factors may occlude real effects.

The few studies that have looked at the interaction of psychological factors with opioid signaling indicate that the actual relationship between social

interactions and the opioid system is likely to be far more complex than has been presented up to this point. For example, in a study of emotional responses to a film clip of a married couple bonding before the birth of their first child, blockade of the μ-opioid receptor with naltrexone prevented feelings of warmth and affiliation, but only in participants who reported high levels of social closeness (a subscale of the MPQ; (Depue and Morrone-Strupinsky 2005). This study preselected participants high and low on this scale which assesses sociability and the degree to which one values close interpersonal relationships. This film not only increased feelings of warmth and affiliation among those high in dispositional social closeness, but also increased their pain tolerance much like the previously mentioned studies that found viewing pictures of one's romantic partner had pain suppressing effects. These pain suppressing effects of watching the film clip were blocked by naltrexone, but only in individuals high in social closeness. This suggests the opioid system functions differentially in those at opposite ends of this personality scale and that those who are lower in social closeness are less able to activate their opioid system. This finding certainly supports the model proposed previously, but if one did not pay attention to these personality effects one could potentially not see an effect of the opioid manipulation.

Another psychological moderator that might be important to attend to studies of opioid mediated social effects is anger regulation style (Bruehl et al. 2009). In particular, those who dispositionally tend to outwardly express their anger, as assessed by the Spielberger State-Trait Anger Expression Inventory (sample items: When angry or furious "I do things like slam doors", "I say nasty things", or "I strike out at whatever is infuriating"), appear to have lower levels of endogenous μ-opioid mediated neurotransmission. When the μ-opioid receptor is blocked by naltrexone, individuals high in anger expressivity show little difference in pain response from placebo, while those who are lower on this scale show marked differences (Bruehl et al. 2002). Follow-up analyses showed that the hyper-response to pain in those high in anger expressivity is partially mediated by this opioid dysfunction (Bruehl et al. 2003). This impaired opioid function in high anger expression individuals is consistent with their heightened cardiovascular reactivity during anger provocation (Burns et al. 2004). Of relevance for epidemiologists and public health researchers, the genetic variant affecting levels of the μ-opioid receptor described earlier (A118G) also moderates the effects of trait anger out on acute pain sensitivity (Bruehl et al. 2008).

In a different strain of research, similar results have been found with a repressive stress coping style. Individuals who are low on this dispositional measure, and presumably high in emotional expressivity, tend to have reduced endogenous opioid signaling as they are more responsive to opioid blockade (Jamner and Leigh 1999). Thus, it appears that those who tend to express their anger and other emotions outwardly may lack sufficient endogenous opioid signaling to inhibit both pain and anger expression, which leads to greater peripheral physiological activation and correlated health consequences. Such individuals may show reduced salubrious effects of social relationships because social interactions may be less able to activate their opioid system. Or, conversely, because of their low levels of endogenous

opioids social relationships may be even more important for individuals who have high anger expressivity. These are naturally questions for future research, but these studies indicate that for a complete understanding of how social relationships impact health both psychological and neurochemical measurements will be necessary.

In summary, opioid mediated neurotransmission is modulated by social variables, and in turn differences in opioidergic function affect psychology and sociality. This bidirectional influence between the neurochemical and psychosocial realms indicates that neuroscientists, public health researchers, and psychologists have much to gain by talking to each other. It also suggests that improved understanding of how individual differences in both neurochemical and psychological function interact can lead to social and environmental interventions that can alter neurochemical signaling in a manner that promotes better health.

Highlights

- Social interactions are the most potent behavioral influence on health
- In spite of extensive research, the psychological mediators of these effects are unclear.
- The quality of one's social connections impacts concentrations of the endogenous opioids, which are neurotransmitters that affect the functioning of peripheral physiological systems that influence health such as the sympathetic nervous system, hypothalamic-pituitary-adrenal stress axis, and the immune system.
- Understanding the interaction between opioid neurochemistry and psychological state is likely to be critical for a mechanistic understanding of social influences on health.

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Chapter 11
Brain Functions Modulating Redistribution of Natural Killer Cells Accompanying Cognitive Appraisal of Acute Stress

Hideki Ohira

Introduction

Studies in psychoneuroimmunology (PNI) have suggested the bidirectional communication between the immune and central nervous systems, which is mediated by neural pathways linking these systems and by expression of receptors for ligands of one system (e.g. cytokines and neurotransmitters) on the cells of the other (Haddad 2008). Generally, the brain has ability of regulation over immune functions, via neural innervation of lymphatic organs (Madden et al. 1995) and expression of receptors for neurotransmitters on immune cells (Tracey 2009). On the other hand, the immune system has the "sensory" function to signal invasion of antigens or infection to the brain via inflammatory cytokines directly entering brain regions which lack the blood–brain barrier and the ascending vagal nerve (Dantzer et al. 2000).

This chapter focuses on the pathway of "top-down regulation" by the brain over immunity. Specifically, the main focus of this chapter is modulation of one of the most rapid and sensitive immune responses to acute stress, that is, changes in the numbers of lymphocytes in blood circulation, accompanying cognitive appraisal of a stressor. Although alterations of immune functions by chronic stress and involvement of brain functions in that are usually more referred to in the context of PNI, dynamic modulation of peripheral immune functions by the brain in acute stress is a good example of brain-immune connection which can work for survival.

In this chapter, the phenomenon of changes in lymphocytes in acute stress is first described. Then empirical findings about effects of cognitive appraisal on immune modulation and their neural correlates are introduced.

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Changes in Lymphocytes Accompanying Acute Stress

Redistribution of Natural Killer Cells

It has been demonstrated that acute psychological stressors lead to changes in distribution of lymphocytes in peripheral blood circulation, which is called redistribution of lymphocytes. This phenomenon plays a key role for organism's survival in a stress situation (Dhabhar 1998; Kiecolt-Glaser et al. 2002).

In humans, it has been known that this redistribution occurs differentially between lymphocyte subsets. Acute psychological stress tasks such as mental arithmetic or public speech usually cause remarkable elevation of the number of natural killer (NK) cells in peripheral blood, while these tasks elicit mixed results in CD3 + T cells: a slight decrease (Kimura et al. 2005), an increase (Adler et al. 2002), or no change (Benschop et al. 1998). Pharmacological blocking studies and in vitro studies suggested the essential role of sympathetic nervous activation in this phenomenon (Benschop et al. 1993).

These studies revealed that the increase in the number of NK cells reflected release of NK cells from several reservoirs such as the wall of blood vessels and the spleen into blood circulation. Also, such redistribution of NK cells was induced by elevation of blood pressure and secretion of catecholamine, especially as a result of the beta-adrenergic effects of epinephrine (Benschop et al. 1994; Crary et al. 1983). This redistribution of NK cells into circulation is explained as a component of "fight-flight" responses for survival in an acute stress situation. Specifically, the selective increase in NK cells that can react to any antigens could work as the effective preparatory defense for potential invasions of bacterium and virus from wounds made in "fight-flight" behaviors (Benschop et al. 1996).

Adhesion Molecule CD62L

This redistribution of NK cells is determined by the expression of adhesion molecules such as CD62L on the surfaces of the NK cells. The cell adhesion molecule CD62L (also denoted as L-selectin) is important in trafficking lymphocytes in and out of blood circulation (Bevilacqua 1993). NK cells with higher density of CD62L can adhere to the vessel wall and lymph nodes more efficiently than NK cells expressing less CD62L (Frey et al. 1998). Bosch et al. (2005) demonstrated that the amount of NK cell redistribution induced by a public speech task was dependent upon the expression density of CD62L. Specifically, NK cells with low density of CD62L were more recruited and NK cells with high density of CD62L were much less mobilized.

We examined in detail the temporal characteristics of redistribution of NK cells, depending on expression of CD62L, in a psychological acute stress situation (Kimura et al. 2008). In our study, participants performed a mental arithmetic task for 10 min as a stressor, and their blood samples were taken at a baseline, 1 min

after the initiation of the task, and every 2 min during the stress task. The elevation of NK cells without CD62L reached to a significant level comparing to a baseline level, at 1 min after the initiation of the stressor, while NK cells with CD62L did not show significant elevation (Fig. 1).

As noted above, the degree of expression of adhesion molecules such as CD62L mechanically determines mobilizability of NK cells. However, interestingly, most NK cells without CD62L are matured cells and show higher cytotoxicity (Cooper et al. 2001). Thus, as a result, rapid (1 min) and remarkable elevation of such a subtype of NK cells is very adaptive for survival under a fight-flight situation. Taken together, redistribution of NK cells is a reasonable and effective response for biological defense under acute stress, thus sensitive reactivity and appropriate modulation of NK cell redistribution might be critical to reduce risks of infectious diseases accompanying acute stress.

Stressor Controllability

Although redistribution of NK cells is itself adaptive, if a pattern of that response of NK cells is stable and rigid regardless of the kinds of stressors and of characteristics of stress situations, it would not be effective. Rather, continuous assessment of environmental demands and dynamic modulation of responses of NK cells are critical for adaptation. Psychological models of stress adaptation (Blascovich et al. 1999; Lazarus and Folkman 1984) have focused on the roles of cognitive appraisal. In particular, controllability of a stressor is one of the important factors

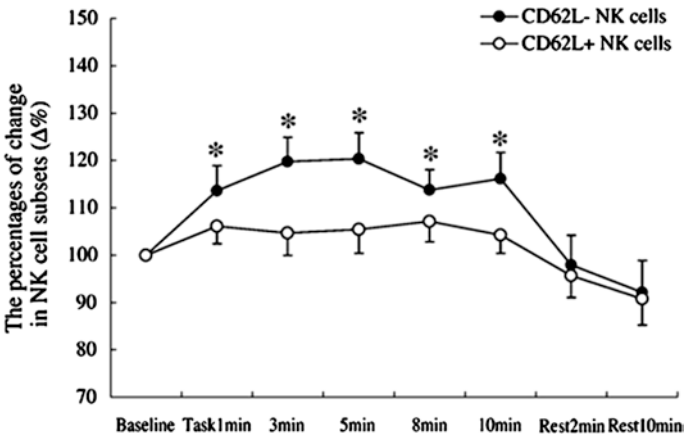

Fig. 1 Temporal changes in percentages of natural killer (NK) cells accompanying acute stress (mental arithmetic task) and its modulation by adhesion molecule CD62L. *Black circles* indicate NK cells without CD62L and *white circles* indicate NK cells with CD 62L. (Kimura et al. 2008)

in processes of cognitive appraisal. Generally, if a stressor is evaluated as uncontrollable, more negative emotions such as depression and anxiety are elicited, and motivation and effort to cope with the stressor are reduced (helplessness).

Effects of Stressor Controllability on NK Cell Redistribution

Several studies have suggested that the autonomic, endocrine, and immune systems can react differently to a stressor according to stressor controllability (Gaab et al. 2003; Maier and Watkins 2005; Peters et al. 1999, 2003). However, these findings are mixed in that some reported enhanced physiological responses to uncontrollable stressors, while others reported attenuated responses to the uncontrollable stressors. These mixed findings are probably due to differences in subjects (humans vs. animals), types and severity of stressor (cognitive tasks vs. electric shock), and experimental manipulation of controllability. Especially, findings on immune modulation by stressor controllability are still rare.

Thus, we conducted a series of studies to examine the effects of controllability of an acute cognitive stressor on redistribution of NK cells as well as possibly mediating autonomic and endocrine responses in healthy human participants. In one of our studies (Kimura et al. 2007), we used a stochastic learning task with time pressure as a cognitive stressor. This task is a kind of gambling, and is typically used in studies on decision making. Participants are presented with two visual stimuli and have to choose one of them to gain monetary reward and to avoid monetary punishment. In this study, one advantageous stimulus was associated with reward at a probability of 70 % and associated with punishment at a probability of 30 %, whereas another disadvantageous stimulus was associated with reward and punishment at reversed probabilities (30 % reward and 70 % punishment). Feedback signaling reward and punishment was conveyed to participants just after their decisions. Of course participants did not know this hidden rule (contingency) and thus they had to find and learn this contingency through trial and error. As the total performance actually influenced the monetary incentive for participants, and as they had time pressure for decision in each trial, this task can work as an acute stressor. In this case, the situation is controllable because participants could appropriately cope with this task (choosing the advantageous stimulus is a right behavior). In addition, we set another condition in this task where a bogus and yoked to feedback signaling reward and punishment was given, thus participants could not learn any appropriate rule to cope with this task. In this case the situation was totally stochastic and uncontrollable. This experimental procedure is corresponding to the typical yoked design commonly used in animal studies. Importantly, this yoked design enabled precise control of the amount of reward and punishment between the controllable and uncontrollable groups, and only controllability could be manipulated.

NK cells remarkably increased at first and then gradually decreased to the baseline in the controllable group while the uncontrollable group showed an attenuated increase in NK cells (Fig. 2). These patterns of changes in NK cells were parallel

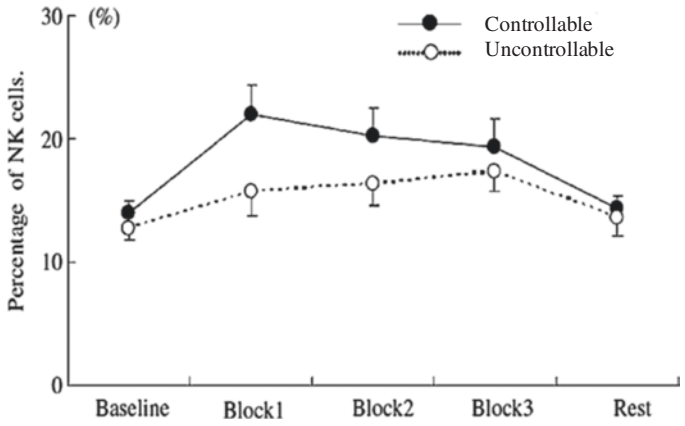

Fig. 2 Changes in percentages of natural killer cells during controllable and uncontrollable conditions in a stochastic learning task. Each block contained 80 trials of the task and lasted for 5 min. (Kimura et al. 2007)

with changes in cardiovascular parameters such as heart rate and blood pressure. Results suggest that NK cell redistribution and possibly mediating cardiovascular reactivity to acute stress can be modulated by stressor controllability. This attenuation of physiological responses including NK cell redistribution in uncontrollable acute stress was also shown in another study from our laboratory where a mental arithmetic task was used as a stressor (Isowa et al. 2006). We interpreted that such attenuation of physiological responses in an uncontrollable stress situation probably reflects a kind of "energy-saving strategy" to prevent wasting of limited biological resources in a situation where the most adaptive form of coping is unclear. Although redistribution of immune cells including NK cells itself should contribute to the adaptation as described above, we found that such immune cells, transiently increased by acute stress, secrete inflammatory cytokines within a short time (20 min; Yamakawa et al. 2009). Because elevation in levels of inflammatory cytokines should lead to higher load for organisms, attenuation of redistribution of NK cells in an uncontrollable situation should also be adaptive.

Neural Correlates of Effects of Stressor Controllability

These findings suggest that hypothalamic or midbrain activities directly controlling peripheral physiological systems may be modulated by higher brain regions to cope with demands from environments. To examine this inference, we conducted a neuroimaging study to examine the neural basis of modulation of NK cell redistribution accompanying appraisal of controllability of an acute stressor (Ohira et al. 2009). For this purpose, we performed simultaneous measurement of brain activity (regional cerebral blood flow: rCBF) using ^{15}O-water positron emission tomography (PET) and

physiological parameters of cardiovascular (heart rate and blood pressure) and neuroendocrine (epinephrine, norepinephrine, and adrenocorticotropic hormone) activities, and also the numbers of NK cells in peripheral blood during the same acute stressor (stochastic learning task) as described above (Kimura et al. 2007). Using this experimental setting, we can examine the pattern of reactivity in each parameter, and additionally can examine brain-physiological coupling by creating a correlation brain map showing brain regions with significant correlations between brain activation and change of a physiological parameter.

Consistent with our previous studies (Kimura et al. 2007; Isowa et al. 2006), the increase in NK cells, as well as cardiovascular responses (reported in Ohira et al. 2010), was significantly attenuated in an uncontrollable stress condition, comparing to a controllable condition. For brain activity, the dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex (OFC) were activated in uncontrollable stress but not in controllable stress. These patterns of brain activation in uncontrollable acute stress were generally consistent with our previous neuroimaging study using a mental arithmetic task as a stressor (Ohira et al. 2008). As the OFC evaluates contingencies between actions and outcomes in both humans (O'Doherty et al. 2001, 2003) and animals (Roberts 2006), the above result might suggest habituation of OFC activity after completion of learning about contingency between stimuli and outcomes in the controllable condition, and continuous effort to seek for the contingency in the uncontrollable condition. The DLPFC is related to the executive function and working memory (Levy and Goldman-Rakic 2000), thus this region should be critical for evaluation of stressor controllability, and thus might be more recruited for search of contingency in the uncontrollable condition.

More interestingly, activation in the DLPFC and OFC significantly correlated with the degree of redistribution of NK cells in the uncontrollable condition, but not in the controllable condition (Fig. 3). On the other hand, activation only in the medial prefrontal cortex (MPFC) which is involved in monitoring of ongoing processing (van Noordt and Segalowitz 2012) correlated with changes in NK cells in the controllable condition (Fig. 3). This is understandable because a situation is evaluated as good and it is enough to recruit the minimum brain region for just monitoring of the current situation in controllable stress. These results suggest that redistribution of peripheral NK cells can be modulated on the basis of evaluation of the controllability of a stressor through functions of plural prefrontal regions such as DLPFC, OFC, and MPFC.

The biological mechanism mediating modulation of NK cell redistribution via the DLPFC and OFC is a focus of much interest, as there is no direct pathway from such higher-order cortical regions to peripheral immune cells. Some theorists have argued that the vagus nerve or parasympathetic nervous system may play a critical role in such flexible regulation of peripheral physiology (Thayer and Brosschot 2005). Because of differences in the temporal kinetics of neuroeffectors, vagal effects occur faster than sympathetic effects (Saul et al. 1990). Thus, the former should be more suitable for fast and delicate regulation. To examine this hypothesis, we measured the high frequency (HF) component of heart rate variability (HRV) as an index of vagal activity during the baseline period and during the stochastic learning task. The result showed that attenuation of the cardiovascular responses in the uncontrollable

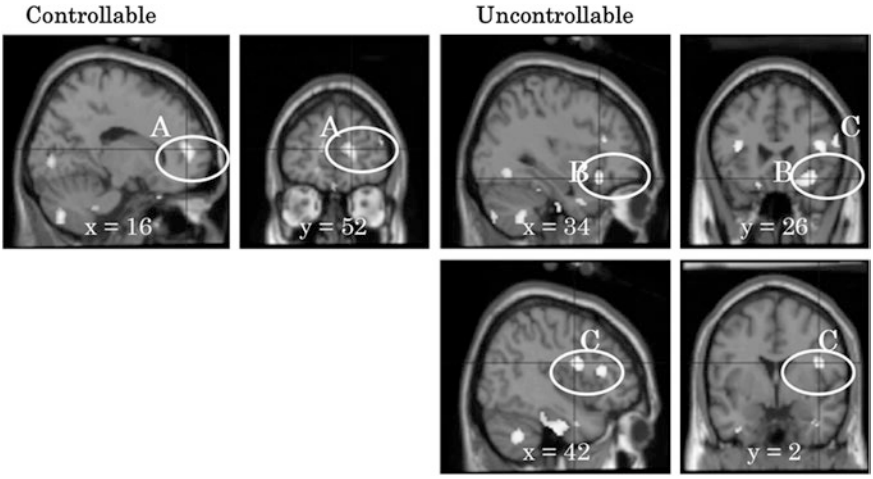

Fig. 3 Correlations between regional cerebral blood flow and natural killer cells in controllable and uncontrollable stress conditions. *A* Medial prefrontal cortex. *B* Orbitofrontal cortex. *C* dorsolateral prefrontal cortex. $P < 0.001$, uncorrected. (Ohira et al. 2009)

condition was caused by enhanced vagal activity (Fig. 4a). Furthermore, a correlation analysis between PET brain images and vagal activity reflected by power of the HF component of HRV indicated that the rostral portion of the anterior cingulate cortex (ACC) might be responsible for the top-down regulation of peripheral physiological responses (Fig. 4b). This result is consistent with a result of a meta-analysis about neural correlates of HRV (Thayer et al. 2012). As cardiovascular activities such as heart rate and blood pressure are main mediators of NK cell redistribution, it might be plausible that the DLPFC and OFC can modulate NK cell redistribution via activity of the rostral ACC and vagal nerve.

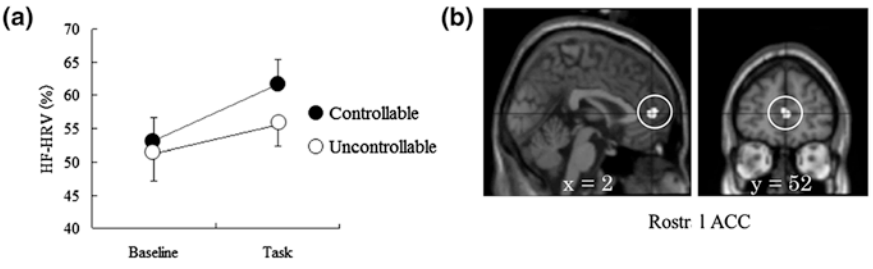

Fig. 4 **a** Changes in high frequency component of heart rate variability (HF-HRV) in controllable and uncontrollable conditions. **b** Correlation between regional cerebral blood flow and HF-HRV in an uncontrollable condition. $P < 0.001$, uncorrected. (Ohira et al. 2009)

As a summary, Fig. 5 shows a simple schematic expression of modulation by the brain over NK cell redistribution. When a stressor is controllable, mainly the MPFC works for monitoring of current processing and coping to stressor is performed on the basis of habit actions. As the situation is evaluated as not severe, physiological responses including cardiovascular activity and NK cell redistribution are regulated in a somewhat automatic way. On the other hand, when a stressor is uncontrollable, the situation is evaluated as more threatening, thus the DLPFC and OFC are recruited for online coping to the stressor. In this case, the rostral ACC is recruited as a hub-center for regulation over peripheral physiology.

Change in Contingency Between Actions and Outcomes

If the prefrontal brain regions can be involved in cognitive appraisal of an acute stressor and can modulate NK cell redistribution on the basis of results of appraisal, such functions of the prefrontal regions might become more dominant in a situation where contingency between actions and outcomes is unstable and uncertain. In such a situation, we have to perform continuous monitoring of the situation, and conduct rapid and flexible changes in coping strategies. Based on mechanisms of the top-down regulation by the brain over peripheral immune cells described in this chapter, it is predicted that NK cell redistribution might be regulated more rapidly and more flexibly in the unstable and uncertain situations.

Vagal Tone Indexed by Heart Rate Variability

From our everyday experiences, it can be predicted that there are wide individual differences in the ability to adapt to an unstable and uncertain stress situation, as it is a difficult task for us. Here, I raise the hypothesis that one of the biological sources of such individual differences of ability in psychological and physiological adaptation to unstable acute stress might be the tonic level of activity of the vagus nerve.

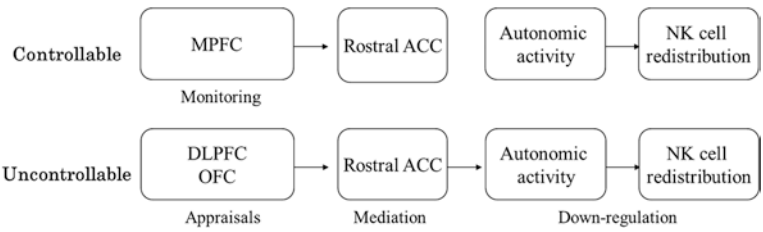

Fig. 5 Modulation of natural killer cells by brain accompanying cognitive appraisal of stressor controllability

As noted above, the vagus nerve is much more sensitive compared to the sympathetic nerve, thus tonic vagal activity is involved in flexible modulation of cardiac activity. Although originally the influence of vagal tone is limited to modulation of the cardiac activity, theorists are elaborating on this finding to a possibility of modulation of other physiological systems such as the endocrine system (Thayer et al. 2012). A further expansion of the notion is that vagal tone indexed by HRV might affect modulation of peripheral immune functions. One rationale of this speculation is a fact that brain regions regulating activity of the vagus nerve partly overlap with brain regions involved in immune regulation, including the MPFC and DLPFC (Lane et al. 2009; Thayer et al. 2012). Given the vagus nerve's strategic location between the periphery and the brain, we hypothesized that vagal nerve activity could modulate immune-brain relations. Supporting evidence for a modulating role of the vagus nerve in multiple homeostatic systems comes from a study by Weber et al. (2010) who showed that individuals under acute stress recovered faster on neuroendocrine, cardiovascular, and inflammatory parameters if their HRV was high. Such multisystem modulation by the vagus may need to take place at higher neural levels. Thus, individuals with higher tonic vagal activity and thus higher baseline HRV may have a qualitatively superior interaction in the brain-immune network than individuals with lower HRV. Specifically, individuals with higher HRV might show more flexible modulation in NK cell redistribution accompanying changes in contingency between actions and outcomes in an acute stress situation.

Modulation of NK Cell Redistribution by Vagal Tone and Its Neural Correlates

To verify this prediction, we (Ohira 2012) conducted a neuroimaging study using the same experimental setting as described above (Ohira et al. 2008, 2009). To simulate the change in contingency between actions and outcomes, we used a stochastic reversal learning task. This task is similar to the stochastic learning task. One advantageous stimulus which was linked with monetary reward at a probability of 70 % and with monetary punishment at a probability of 30 % and other disadvantageous stimulus which was liked with reward at a probability of 30 % and with punishment at a probability of 70 % were presented to participants, and they performed decision making to get reward and to avoid punishment (initial learning). However in this task, the contingency between stimuli and outcomes was suddenly reversed in the middle of the task without any explicit instruction to participants. Thus, they had to suppress the dominant behavioral tendency to choose the previously advantageous stimulus, and had to re-learn the new contingency (reversal learning). This task was to require cognitive flexibility (Kehagia et al. 2010). Two groups of participants with high HRV and low HRV performed the three blocks for initial learning (120 trials in total) and an additional three blocks for reversal learning (120 trials in total). Their brain activity was evaluated by ^{15}O-PET and their NK cell redistribution as well as changes in helper T cells as a control parameter during each block was assessed.

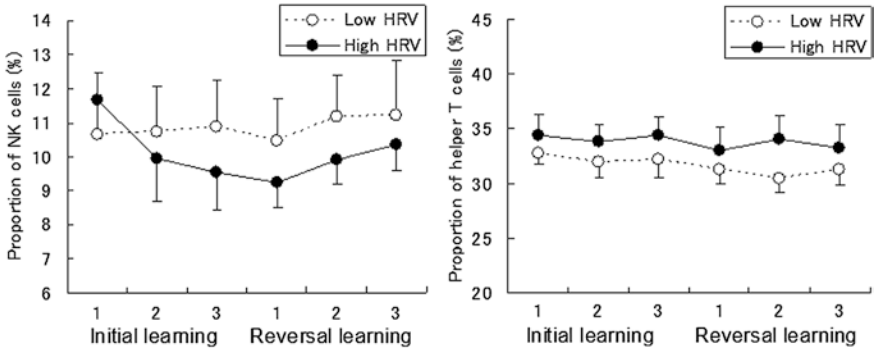

Fig. 6 Changes in proportions of natural killer cells and helper T cells during a stochastic reversal learning task in high and low heart rate variability (HRV) groups. (Ohira 2012)

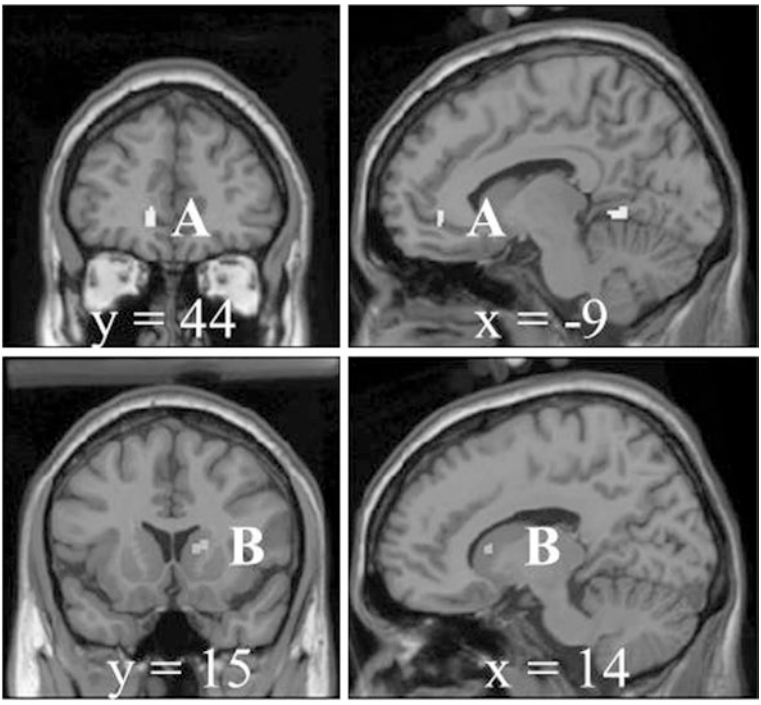

Fig. 7 Correlations between regional cerebral blood flow and natural killer cells in a high heart rate variability group. *A* rostral anterior cingulate cortex, *B* striatum (caudate). $P < 0.001$, uncorrected. (Ohira 2012)

Figure 6 shows changes in NK cells and helper T cells during both initial and reversal learning in the high and low HRV groups. The two groups indicated apparently a differentiated pattern of changes in NK cells. Specifically, NK cells in

the high HRV group showed a gradual decrease during initial learning which probably reflected habituation, and then showed an increase after introduction of reversal of stimuli-outcomes contingency which probably reflected re-mobilization due to exposure to a new stressor (reversal of contingency). However, the low HRV group showed no changes in their NK cells both during initial learning and reversal learning. No change in helper T cells in both groups suggests that the differentiated influence of the stressor between the high and low HRV groups was specific to NK cells which are the most sensitive immune cells to acute stress.

To examine the neural basis of this phenomenon, we created correlation maps between brain activity and NK cell redistribution both in the high and low HRV groups (Fig. 7). Only the high HRV group showed significant correlations between changes in NK cells in each block and brain activation in the rostral ACC and dorsal striatum (the caudate). Importantly, these two brain regions consist of the core system of neural basis of HRV (Thayer et al. 2012). Therefore taken together, individuals with high HRV have more ability of flexible modulation of NK cell redistribution in an unstable and uncertain acute stress situation, and such ability might be due to sensitivity of the ACC and striatum which can control peripheral physiology via modulation of activity of the vagus nerve. What factors determine individual differences in vagal tone indexed by baseline HRV is an open question to be clarified in future studies.

Conclusions

The empirical findings described in this chapter lead to the following conclusions. First, the number of NK cells in peripheral blood circulation rapidly increases during acute stress. This phenomenon is called redistribution of NK cells and is mediated by autonomic and cardiovascular activities. Additionally, this phenomenon might have adaptive functions for biological defense and survival in acute stress situations. Second, plural prefrontal regions of the brain can evaluate controllability of a stressor and can rapidly modulate redistribution of NK cells via autonomic activity, on the basis of the appraisal. Third, the prefrontal regions of the brain can flexibly evaluate the demands of an unstable and uncertain stressor, and lead to habituation or re-mobilization of physiological activities, including redistribution of NK cells. Vagal tone indexed by HRV can be a promising index of ability of such top-down regulation by the brain. Additionally, the rostral ACC and striatum might be the neural source of such flexible modulation of NK cell redistribution in the unstable stress situation.

Ability of flexible tuning of immune functions such as NK cell redistribution should be a key factor for prevention of infectious diseases and some chronic diseases such as heart disease, cancer, and diabetes. In this context, reactivity of NK cell redistribution and its neural correlates can provide useful indices of risks for the diseases. Recently, we reported that chronic job stress measured by high job demand and low job control (Karasek et al. 1998) was linked to reduced activation of the prefrontal cortex in a reversal learning task and blunted cardiovascular reactivity (Ohira et al. 2011). This finding suggests that chronic exposure to uncontrollability in a

social scene might lead to poorer neural and cardiovascular reactivity to acute stress, probably linked with less reactivity in immune responses such as NK cell redistribution. Such dysfunctional brain-immune reactivity might be a mediator between social factors such as job stress, socio-economical status, and social exclusion and several diseases. Furthermore, interventions to improve sensitivity of NK cell redistribution and possibly mediating vagal tone might be effective for treatments and prevention for the disease. These are open questions to be examined in future studies.

Highlights

- Natural killer (NK) cells in peripheral circulation rapidly increase (redistribution) in acute stress and can facilitate preventive defense.
- NK cell redistribution can be modulated based on cognitive appraisals of stressors, reflecting flexible adaptation to the stressors.
- The prefrontal cortex of the brain is involved in appraisals of stressors and in top-down modulation of NK cell redistribution via the vagus nerve.
- Functional connection of the brain and immunity should be critical for facilitation of health and prevention of diseases.

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Chapter 12
Alzheimer's Dementia and Lifestyle: Towards a Primary Prevention

Harald Walach and Martin Loef

Introduction

In 2010, 35.6 million people worldwide suffered from dementia, with 60–80 % of all cases being Alzheimer's type dementias. In 2050 it is estimated that figures will rise to 115 million, a 225 % increase (Alzheimer's Disease International 2010). Worldwide costs are estimated at US-$ 604 billion every year (Luengo-Fernandez et al. 2011). These figures are bound to rise with a growing world population, with an increase in life expectancy, and with the simultaneous growth of an important risk factor of dementia, obesity, and metabolic syndrome, whose incidence is also on the rise (Wang et al. 2011; Loef and Walach 2012d). Including this trend in the extrapolation of future incidence figures increases the estimates by 9–19 % for the US and China, respectively.

The pharmacological era, conceptualized as a consensus that medical success and breakthroughs in the fight against major diseases will come from the development of new pharmacological agents, is slowly drawing to an end, we feel. This analysis is fueled by the lack of success in pharmacological breakthroughs in general over the past few decades, specifically for the treatment of dementia (Roberson and Mucke 2006; Mangialasche et al. 2011). All big pharmaceutical companies have invested multi-billion sums into the development of new agents, and only four substances have made it to market, providing only small clinical benefits with large numbers needed to treat, a high risk of unwanted side effects, and no effective clinical stopping rule (Howard et al. 2012). Usually, mono-causal theoretical models of the disease have been used as a template for the development of treatment (De la Torre 2011), such as the model that Alzheimer's disease is due to the abnormal production of the protein amyloid beta, or the dysfunction of the

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axonal trafficking and consecutive destruction of the microtubular skeleton of neurons due to hyperphosphorylated tau protein, or the fact that mainly acetylcholinergic neurons are affected, especially in initial phases of the disease. The lack of success of pharmacological treatments following such mono-causal models speaks to the fact that they are too simplistic to really capture the complex interactions of causes and mechanisms. More importantly, it is unclear, whether the accepted clinical signs and symptoms of the disease, such as amyloid plaques and fibrillar tangles in neuronal tissue followed by neuronal death and neuro-inflammation, due to amyloid-beta production and hyperphosphorylation of tau, are really the cause or perhaps only the effects of more complex processes. Interestingly, post-mortem studies with victims of traffic accidents have shown that these purported pathognomonic signs of AD are also present in some young people who did not have clinical signs of dementia (Braak and Del Tredici 2011; Braak et al. 2011). Furthermore, in old people most of these signs can be observed without the clinical specificity of AD (Snowdon 1997). The current attempt to develop vaccines against these potentially pathological proteins is only effective in animal models (Janus et al. 2000), but not clinically (Morgan 2011).

The path laid out by the cholinergic hypothesis has not been fruitful either. The hypothesis that AD is due to the gradual destruction of cholinergic neurons in the basal forebrain was proposed as early as 1982 (Bartus et al. 1982). This system is crucial for focusing, memory building, and retrieval processes (Hasselmo and McGuaghy 2004). While a loss of cholinergic neurons and fibers concomitant with AD progression is certainly well documented by now (Schliebs and Arendt 2011), it is unclear, whether this loss of cholinergic neurons is the cause or the result of the disease process, or, again, just an accompanying feature (Contestabile 2011). Since pharmacological strategies targeting this process, either by inhibiting the actylcholine-esterase enzyme or by reducing toxicity from glutamatergic activity through NMDA-receptor antagonists have resulted in only minor clinical benefits, this model cannot be telling the full story either (Nyakas et al. 2011; Howard et al. 2012).

Although some genetic markers, such as the apolipoprotein ε-4 allele, have been identified as risk factors (Farrer et al. 1997; Wisdom 2009), their explanatory and predictive values are far from sufficient.

It might well be the case that the attempt to find a pharmacological fix for a disease that likely starts decades earlier before it becomes symptomatic was, pragmatically speaking from a public health point of view, the wrong strategy altogether (Hofman et al. 2006). While we have learned a lot scientifically, this knowledge has not translated in a single case of death from Alzheimer's disease prevented. It is unknown whether it has increased the life-expectancy of patients, or their quality of life. Furthermore, it might well be the case that this strategy has actually introduced false differentiations. While the pathological pictures at the end of long disease histories might be different, the initial processes that trigger the clinical pathology might be very similar across various forms of dementia, even across various forms of chronic diseases. Looking at diseases as long-term temporal Gestalts they might be conceptualized as complex interactions of lifestyle choices that trigger epigenetic changes through interactions with the

environment and lead to pathological changes that, depending on a particular set of genes, expository risks and behaviors, then cause pathological processes that are dissimilar at the distal end, but very similar at the proximate starting point (Whalley et al. 2006).

We take this as a starting point for our deliberations and ask: What kind of lifestyle might be able to prevent the outbreaak of dementia as a disease? What evidence do we find in the literature that certain lifestyle factors are associated with dementia, in particular AD? What recommendations regarding lifestyles and public health measures can be derived with reasonable certainty. The catchphrase here is "reasonable certainty". While some only accept the purportedly "highest degree of evidence", randomized controlled trial (RCT) evidence, as "scientific" and allowing for unbiased, certain conclusions, we take a more liberal and pragmatic stance here. Dementia, as an impending, worldwide public health disaster, demands for action in the face of uncertainty. Direct experimentation with humans, as in RCTs, is hugely restricted in terms of observational follow-up time, ethics, practicality, and funding. Thus, short, small, and selective RCTs provide evidence with a lesser degree of usefulness and certainty than large-scale, long-term, and population wide reaching observations. What is lacking in mechanistic insights from human studies can often be gleaned from animal models. This is the reason, why we have decided to opt for multi-method and multi-disciplinary reviews to screen the literature. We are deriving suggestions for lifestyle changes and interventions from evidence that is less than perfect. We do this on purpose, following the reasoning of a wager similar to the classic one that Pascal used to demonstrate the viability of the concept of god. We wage that, given we have to face uncertainties here, if our suggestions are wrong, because the evidence we are using is still too weak, they would not do much harm. But if our suggestions are correct then the potential gain is huge, because the question at hand is so important. Thus, conservative minds will find the basis for some of the proposals we make too frail. Our rejoinder is: we do not have the time and the means to wait until firm evidence compels us to conclusions. Thus, an expert conference of the National Institutes of Health, taking a more conservative and rigorous position, has concluded that there is not enough evidence for promoting prevention (Daviglus et al. 2011). We follow a number of research groups and Alzheimer's associations that have contradicted this conclusion (Woodward 2007; Middleton and Yaffe 2010; Mangialasche et al. 2012).

It is an interesting and well-established fact that members of populations with a lower risk of AD, such as Japanese people, increase their risk of AD when they move to the US (Graves et al. 1999), or genetically identical people, such as the Yoruba in West-Africa and black US-Americans have significantly diverging risks (Hendrie et al. 2001). This seems to point to the importance of lifestyle and food. We know that a lot of the brain areas suffering damage in AD are the same as those comprising the so-called default mode network, a network of brain areas that produce the baseline activities of the brain (Roberson and Mucke 2006). Thus, this network seems to be especially vulnerable in AD patients, perhaps because of a basic hyperactivity. Hence, activities targeting this network, such as relaxation and meditation exercises, might be useful. The role of omega-3 fatty acids for neuronal

repair and growth processes has long been known. It is also known that the ratio of omega-3 to omega-6 fatty acids in the Western diet has dramatically changed over the last century (Simopoulos 2011), while the load of environmentally produced toxic substances has also increased.

Thus, in what follows we describe elements of lifestyle interventions that are aimed at modifying those aspects that are most important according to our reviews. Not very surprisingly, the resulting program sounds rather generic, since a primary prevention program for most chronic diseases will contain most of these elements. The specificity, however, lies in some single components and its innovative feature is the idea to not use it like a medication, given to everyone in the same dosage, but to adapt it individually to specific situations and to find individually suitable modifications that are sustainable over the life span.

Elements of a Primary Prevention Program

The proposed modules of our prevention program consist of

1. avoidance of smoking and toxins, such as lead, mercury, aluminum, and reducing intake of potentially harmful trace elements such as iron and copper
2. the adaptation of nutrition: micronutrients such as omega-3 fatty acids, but also the provision of phytochemicals that serve as free radical scavengers (derived from fresh vegetables and fruit), combined with a restriction of calorie intake in order to prevent insulin resistance of neurons and to prevent a pro-inflammatory cascade
3. the adoption of a practice of "culture of consciousness" that targets the hyperactivity of the default mode network and helps balance stress
4. physical exercise and an active lifestyle
5. participatory activities and social inclusion in networks, and social relationships that are supportive and fulfilling.

Avoidance of Toxins

Over the years a lot of single substances have been implicated as a potential cause of AD and other neurodegenerative diseases. There is no single toxin that can be pinpointed as a typical cause for any disease, except lead induced encephalopathy. Causal agency that can be demonstrated for some agents in basic research systems, cannot be translated to humans, as the complexity of human physiology and its nonlinearity as a resulting property makes predictions next to impossible and allows for an extremely wide range of ways in which humans respond to one and the same agent (del Sol et al. 2010; Pincus and Metten 2010; Barabasi et al. 2011). The problem is often the action of small or very small doses of toxins over a long time, often in conjunction with co-factors.

Mercury

One such substance is mercury, especially metallic mercury. In a systematic and interdisciplinary review, we found that while mercury can produce all the signs of AD in cell cultures and animal models, the association between mercury exposure and AD in clinical cases was loose and often counterintuitive (Mutter et al. 2010). There is a clear, albeit weak, relationship between mercury exposure, and memory and attention function in people exposed to mercury. There has been a steady influx of mercury, both inorganic and organic, into the natural environment from the middle of the nineteenth century onwards, as a consequence of industrial production, usage in dental amalgams, as a preservative, and in various domestic uses, including energy saving light bulbs. Its main potential as a promoter of AD might be the fact that in the human brain, mercury binds to selenium, which is one of the body's principal detoxification mechanisms against mercury intoxication. Since selenium is also one of the most important elements in the brain's redox balance, buffering oxidative stress, it is a very reasonable scenario that an organism either challenged with low doses of mercury over a long period or with various short-term high-dosages, can buffer these with selenium only for a limited period, and once a threshold is reached, a cascade of inflammatory processes is started due to rising oxidative stress. Thus, watching a sufficient selenium intake, either by eating food rich in selenium, such as sea fish, Brazil nuts, and flour from selenium-rich soils might be a good strategy, or else supplementation (Loef et al. 2011). Avoidance of mercury is one useful element for a generic prevention program for AD. This affects various aspects of public health, such as political measures to restrict the circulation of and subsequent environmental pollution with mercury, and the gradual fading out of this toxic metal from dental repair work. Where repair work is required, alternative materials should be considered, and selenium supplementation might be considered as a temporary measure to buffer overload with mercury during such procedures.

Lead and Aluminum

Two other potentially dangerous substances with a well-known neurotoxic profile are lead and aluminum (Loef et al. 2011). Aluminum plays a role as additive in vaccines, where its use should be re-considered, as well as in cooking utensils. Lead is still used in some piping in older buildings, where replacements might be indicated.

Smoking

A systematic review and meta-analysis that includes studies up to 2007 found that current smokers had a 50 % higher risk of suffering from AD than a non- or never-smoker (Peters et al. 2008).[1]Most recently, Rusanen et al. (2011), analyzed the

[1] This is confirmed by our own meta-analysis that included studies up to 2011, as yet unpublished.

effects of smoking in relation to the packs smoked per day (Rusanen et al. 2011). They found a dose-dependent effect, with the risk of AD nearly doubling for persons smoking more than 2 packs per day. Importantly, there is no difference between those who never smoked and those who stopped smoking up to approximately 10 years on average before the study began.

Nutrition and Micronutrients

Plant-Derived Antioxidants

A very reasonable and generic suggestion that is well supported by epidemiological studies, is the ample provision of food containing phytochemicals with antioxidant capacity. We know today that plants, especially fresh and colorful ones, with dark green and red colors, contain hundreds of such substances, only few of which have been researched so far. Knowing that one of the pathological mechanisms not only of AD, but also of many other chronic diseases, is a shift of balance in the pro- and anti-inflammatory status toward inflammation, and that this shift increases oxidative stress and oxidative damage, increasing the provision with antioxidants is evidence based (Loef and Walach 2012c), but not through single element vitamins (Tabet et al. 2008). While in natural sources the synergistic effect of hundreds of such substances is active, single substances, such as vitamin C, only play a minor role. Green leafy vegetables in particular seem to be more important than fruit. This might be due to the fact that fruit is often a considerable source of sugars, increasing the levels beyond the usually high intake of carbohydrates in Western societies. Another reason might be that vegetables are often eaten or prepared with fat, which allows the body to absorb lipophilic vitamins and antioxidants, such as vitamin E.

In addition to well-researched sources of antioxidants, such as green tea (Dragicevic et al. 2011) or red wine (Orgogozo et al. 1997), are those which are significantly under-researched, such as mustard, almonds, and other nuts. Whole fruit and vegetable extracts are available as alternatives (Roll et al. 2010).

Omega-3 to Omega-6 Essential Fatty Acid Balance and Fat Intake

Fats have received bad press, mainly through prevention campaigns against cardiovascular disease. The crude formula of "less fat is healthy" is erroneous in its simplicity, and the collective lowering of lipids through lipid lowering drugs on a grand scale needs to be reconsidered with care, especially in the light of the fact that the effect sizes of the preventive effect of such action is very small (Penston 2003; de Lorgeril et al. 2010) and lipid lowering drugs also inhibit essential enzyme production processes such as Co-enzyme Q10 (Littarru and Langsjoen 2007). The balance between the two main types of essential polyunsaturated fatty acids (PUFAs), the omega-3 and omega-6 PUFAs, might be crucial. Neuronal membranes, axons, and cell organelles

contain a high amount of phospholipids of which omega-3 and omega-6 PUFAs are important components, and all neuronal recovery processes are crucially dependent on the availability of omega-3 PUFAs (Lerman 2006; Cole et al. 2009).

Omega-6 PUFA are converted to prostaglandins, leukotrienes, and further products that have atherogenic, inflammatory, and prothrombic effects (Schmitz and Ecker 2008). In contrast, omega-3 PUFAs have anti-inflammatory functions. The balance of intake between omega-3 and omega-6 PUFAs in the Western diet was around 1:1 for a very long time. In the decades after World War II it has shifted to a ratio of 1:15 in Europe and 1:20 in the US (Moffett et al. 2009). This is of relevance, because both PUFA types compete for rate limiting enzymes (Lewis et al. 1990; Dubois et al. 1998). The result of an imbalance leads to a long-term increase of pro-inflammatory cytokines, thus making pro-inflammatory responses more likely and downregulation of inflammatory processes more difficult. Furthermore, a lack of omega-3 PUFAs also means that neuronal repair and growth processes are hampered.

Indeed, our review found that high consumption of fish, one of the major sources of omega-3 PUFAs, is associated with a lower incidence of dementia (Loef and Walach 2012b). While, again, clinical trial evidence of supplementation is equivocal, the epidemiological record and basic research evidence is clear cut. In models of AD, Omega-3 PUFAs protect neurons and animals from damage, and can even repair it, and in most epidemiological studies a higher intake of omega-3 PUFAs through fish is associated with less cognitive decline and dementia incidence. Although it is true that omega-3 PUFAs are mainly derived from fish, they stem, in fact, from alpha-linolenic acid, which is enriched in the chloroplasts of green leafy vegetables (Simopoulos 1991) such as algae, herbs, and salads such as purslane (Simopouloes et al. 1992). Thus, cheese from cows grazing in areas where they can accumulate omega-3 PUFAs, such as Alpine cheese, will contain a lot of omega-3, while cheese from industrial production would not (Hauswirth et al. 2004). Omega-3 intake can be increased. Some lifestyle modification programs achieve this with supplementation of up to 3 g of omega-3 per day (Ornish et al. 2005). Second, omega-6 intake can be decreased. This can be achieved by reducing fat from animal sources, especially if the animals have not been kept in their natural environments, by reducing some plant oils such as olive, sunflower, peanut, pumkin, corn, thistle or wheat germ oils which contain mainly omega-6 PUFAs, and by increasing flax, granola, and walnut oil, which contain more omega-3 PUFAs. Thus, one lifestyle advice seems to be quite well founded: increase the intake of omega-3 PUFAs relative to omega-6, and decrease omega-6. A target of 1:4 ratio of omega-3 to omega-6 PUFAs is being discussed as both necessary and realistic (Simopoulos 2006).

What has emerged across disciplines as a hazard generally, are trans-unsaturated fatty acids, particularly in people with low PUFA intake (Morris et al. 2003). In nature, nearly all unsaturated fatty acids contain the cis-configuration which is modified by partial hydrogenation to saturated fats or to those with trans-configuration (Emken 1984). Consumption of hydrogenated fats, in particular has increased continuously over the last century, importing a number of negative health effects without any known nutritional benefits (Ascherio and Willett 1997). For instance, trans-unsaturated fats increase low-density lipoproteins levels and decrease the

levels of high-density lipoproteins. Thus food that is fried in the wrong type of fat, or in fats that are overheated, is problematic, as are certain types of margarine or purportedly healthy fat replacements containing dehydrogenated fats. As using PUFAs for frying creates trans-fats, it is recommended that short- or middle-chain fats, such as palm or coconut fat, be used for frying.

Carbohydrates and Diet Restriction

A rather new development is the insight that AD might be a form of diabetes, where neurons become insulin resistant (de la Monte and Wands 2005, 2008; Grosman and Picot 2009). Of note, insulin also increases the production of amyloid beta and triggers pro-inflammatory processes, while the hippocampus expresses many insulin receptors, testifying to the importance of insulin also in the brain (Marks et al. 1990). Thus, growing insulin resistance of neurons correlates with a lot of the features observed in AD, such as hyperphosphorylation of tau, increased production of amyloid beta, and an increase in oxidative stress as a result of mitochondrial dysfunction (Neumann et al. 2008).

That insulin resistance plays a role is supported by the observation that diabetes type 2 increases the risk for AD, and treatment of such diabetes type 2 decreases it (Hsu et al. 2011). Since neurons, apart from activating glycolysis, can also generate energy from ketone bodies, one long-term prevention strategy and alternative treatment strategy for AD might be to restrict carbohydrate and sugar intake to prevent insulin resistance of neurons, and to trigger the generation of energy from ketone bodies that are produced in the metabolic breakdown of fat storage. Here, middle-chain fatty acids, such as are contained in coconut products and in butter, might play a role. To our knowledge, this has not been researched to date.

Apart from the fact that restriction of caloric intake is, if moderate, a good preventive health measure in general (Fontana and Klein 2007), there is also evidence specifically supporting its role in the prevention of cognitive decline (Martin et al. 2006; Witte et al. 2009). Thus a very simple and generic lifestyle advice would be to be mindful of calorie intake in general and of the intake of easily degradable carbohydrates in particular. This is, of course, generic advice that has already been issued for cardiovascular treatment and prevention programs, and for cancer prevention programs (Ornish et al. 1998; Ornish et al. 2005; Ornish 2009). A shift of energy intake from carbohydrates and sugar toward wholesome fats is advisable in the light of these findings, but would also need further elucidation.

Other Micronutrients

Selenium was previously mentioned as a trace element essential for guaranteeing the brain's redox-buffering capacity. It is therapeutic within a small range, and if taken in too high a dose over too long a time it can be toxic. But the naturally supportive range is considered by many to be difficult to reach in our current diet,

as natural soils in certain areas of Europe, China and the US are poor in selenium, which is crucial for maintaining antioxidant capacity in the brain (Loef et al. 2011), especially in the light of a potential load with mercury (Mutter et al. 2010). Hence, particularly in older age, occasional supplementation with selenium might be useful. The homeostasis of iron, copper and zinc are crucial for normal neuronal functioning, but only within small windows (Frederickson et al. 2000; Zatta et al. 2009).

As a supplement, iron should only be used in defined situations, such as anemia, as it also increases oxidative stress. Iron is contained in large amounts in red meats, and a logical consequence would be to restrict one's intake of red meats (Sinha et al. 2009). Copper is another substance often contained in multi-substance formulae of food supplements which, in the light of our review (Loef and Walach 2012a), might be damaging rather than helping in respect to AD. In the case of zinc, it might be speculated that a subclinical deficiency, often seen in vegetarians and elderly people, increases the risk for AD (Loef et al. 2012a). With the exception of iron, the evidence remains inconclusive. The role of a number of vitamins in lowering the risk of AD are under discussion, in particular, calciferol (Annweiler et al. 2009), tocopherol (Isaac et al. 2008) and the B vitamins (Dangour et al. 2010). Let us give more details for one example: Homocysteine, a waste product of human metabolism, is normally recycled into methionine or converted to cysteine during the activated methyl cycle. If that methylation process is ineffective or compromised, homocysteine levels rise. Since homocysteine is also neurotoxic, it was implicated as a potential causative agent (Mulder et al. 2005) and has indeed been found to be raised in a longitudinal study of Alzheimer cases. Vitamin B12 and folate contribute to activating the methyl cycle and thus reduce homocysteine (Clarke et al. 1998). Homocysteine can also lead to an increase of amyloid beta and tau (Sontag et al. 2007). Indeed, one systematic review showed that Alzheimer patients had higher levels of homocysteine and lower levels of B-vitamins (van Dam and van Gool 2009). The longitudinal study of the Oxford OPTIMA cohort showed a clear relationship between baseline homocysteine level and cognitive decline, an effect that was also seen in the Rotterdam study's imaging component, where high homocysteine level and hippocampal atrophy was related (den Heijer et al. 2003). While supplementation of folic acid leads to a reduction in homocysteine (Luchsinger and Mayeux 2004; Trialist-Collaboration 2005), this was not always accompanied by improvements in cognitive performance (McMahon et al. 2006; van Dam and van Gool 2009). Again, this might be a function of treatment onset: if used as a therapeutic treatment, homocysteine lowering might not be able to reverse pathological processes that have already started earlier on. But as a preventive treatment it might be useful. However, as such, it has not been studied to date (Coley et al. 2008). In the light of these findings, however, supplementation of vitamin B12 and folate might be wise, especially if homocysteine levels are high.

In addition to single nutrients, nutritional patterns such as the Mediterranean diet have been reported to be associated with a decreased risk of dementia or mild cognitive decline (Feart et al. 2009; Scarmeas et al. 2009), thus supporting an integrative dietary change rather than the preventive supplementation of selected nutrients.

Culture of Consciousness, Stress Management

When observing some business cultures, the phenomenological parallelism with AD symptomatology on a collective-cultural level seems obvious: the overload of information through multiple incoming channels, the speeding up of information processing because of high-throughput demands, and the assumed benefit of multi-tasking, lead to an inability to focus and cognitive underperformance. The hypothesis seems warranted that AD is not only a medical problem of our time, but also a cultural problem that finds a medical expression later in life. While younger people are able to cope with the high demands on their cognitive capacity, somewhere down the line this capacity is ever more challenged and then breaks down. Perhaps we could benefit from viewing AD also as a medical signature for a time and a culture that has speeded up all processes and is cognitively overloading its members, who, in turn, have not learned to cope with this demand. A result of this situation is rising stress levels and burnout, which, typically, also shows itself in memory problems. It has long been known that the hippocampus is one of the brain structures with glucocorticoid receptors. If cortisol levels are too high, atrophy in the hippocampus can be observed, which is relevant for various psychiatric diseases such as depression (Bremner et al. 2004; van Praag et al. 2004; Kudielka and Kirschbaum 2007; Mössner et al. 2007; Hains and Arnsten 2008; Pütz 2008), and might also be relevant for AD. Indeed stress across the lifespan is associated with AD with a hazard ratio of 1.6, such that with three episodes of long-term stress the hazard ratio rose to 2.51 (Johansson et al. 2010). Thus, the hypothesis is quite plausible that learning to manage stress and deal constructively with the cognitive overload that our culture provides us with is a useful measure within a multimodal package to prevent AD. One way of instituting such a "culture of consciousness" (Metzinger 2006) is to teach people a mindfulness or meditation program, relaxing the body and the mind, and carefully observing one's own reactions. Meditation and relaxation are different in effects and effects sizes (Sedlmeier et al. 2012).

Why meditation, and not just relaxation, might be important, is supported by three further observations:

1. The basal fore-brain, the structure implicated in the early stages of AD (Teipel et al. 2005; Grothe et al. 2010), non-specifically provides all those brain centers that are active with an enhancement of activity, while it decreases the activities of neighboring centers (Hasselmo and McGuaghy 2004). Phenomenologically speaking, this capacity to focus and thus relegating intended content to short-term memory, work-space memory and then long-term memory is what is compromised in AD. Of note, a recent imaging study with Zen practitioners and age matched controls has shown that both the cognitive decline over time and the deficit in attention common in older participants are not visible in Zen practitioners (Pagnoni and Cekic 2007). Other morphometric imaging studies have shown that in participants with mindfulness training, hippocampal volume is larger compared with age matched controls (Lazar et al. 2000; Hölzel et al. 2007a, b, 2011).

This is not just incidental correlation, but has also been shown in a longitudinal study (Hölzel et al. 2009).

2. One way of considering meditation is as a method of reducing the activity of the default mode network (Gusnard and Raichle 2001; Raichle et al. 2001; Mason et al. 2007). This has been shown in an imaging study (Pagnoni et al. 2008). The activity of the default mode network is likely the neural correlate of mind-wandering (Smallwood and Schooler 2006). Meditation, it is hypothesized, acts on this mind-wandering phenomenon and helps monitoring it, thus improving affect. From a neurobiological viewpoint, it does this by reducing default-mode network activity. It is interesting to observe that the structures implicated in AD largely overlap with the default mode network, and it has been suggested that AD, among others, is a result of the hyperactivity of the default mode network (Roberson and Mucke 2006). If that hypothesis is warranted, then learning to meditate would help by cultivating consciousness and preserving cognitive capacities.
3. Through meditation, "meta-cognitive awareness" is being installed (Smallwood and Schooler 2006). Such meta-cognitive awareness is not just a strategy; it is a durable capacity to discover, early on, situations that are unwholesome and need changing. Thus it equips people with the tool to anticipate situations that are prone to produce stress and burnout before they can become dangerous. In this way it can help in installing a culture that is conducive to health in a general sense.

Taking all of these points into consideration, we would consider a comprehensive culture of consciousness, involving a set of practices, the prime tool of which would be a meditation practice, as an important component in a preventive program. While there is a lot of evidence for the clinical efficacy of mindfulness-based programs in general for the treatment of some psychological and physical diseases (Grossman et al. 2004; Fjorback et al. 2011; Keng et al. 2011; Fjorback and Walach 2012), there are no reliable data existing, to our knowledge, that documents the effect of meditation in the prevention of cognitive decline.

Exercise

Exercise is among the lifestyle elements whose positive benefits are best supported by evidence. Whatever disease one is looking at, being active and exercising is therapeutic and preventive (Thompson et al. 2003; Shaw et al. 2006; Thomas et al. 2006; Warburton et al. 2006). In our systematic review and meta-analysis of 16 prospective studies with 30,774 patients (Loef and Walach 2012e) we updated and extended an earlier work (Hamer and Chida 2009). We found that exercise also reduces the risk of dementia and AD by approximately 30 % when the highest quintile is compared to the lowest. While an active lifestyle in general is helpful, it seems that moderate to intensive activity conducted several times a week is most effective in the prevention of dementia. Although daily walking of a mile or more also has some effect, there is a clear dose–effect. This supports the

general recommendations of the WHO which includes at least 150 min of moderate physical activity per week for the elderly, ideally 300 min (WHO 2011).Thus one should not only encourage everyday activities, but also the inclusion of participation in a sport as a hobby, performing moderate physical activity on a regular basis. It seems more important to instal regular periods of activity than to merely conduct everyday activities such as cooking or climbing stairs.

Social Inclusion and Relationships

Psychosomatic researchers have observed that in Alzheimer cases, compared with other forms of dementia, many of those who developed the disease lived in social situations that deprived them of healthy participation, shared decision-making, and supportive relationships (Bauer et al. 1998; Bauer 2002). These included, for example, work environments that were threatening and unsupportive, or unhealthy intimate relationships or partnerships, with subsequent withdrawal. In addition, living with a partner in midlife protects against cognitive impairments in later life (Håkansson et al. 2009) and people who engage in social activities during midlife have a lower risk of dementia (Saczynski et al. 2006).

Hence social inclusion should be part of a comprehensive prevention program for all kinds of chronic diseases, including dementia (Cohen 2004).

What Does Lifestyle Mean?

Implicitly, the term “lifestyle” is often used as a pool of behaviors that each can be unconditionally adopted if the individual chooses to. Considering the great obstacles that have been experienced when trying to make people adhere to lifestyle changes with various indications, one might question the concept. Medical sociologists have defined a healthy lifestyle as patterns of behavior based on decisions which depend on multiple factors such as socio-economic status, age, gender, health literacy, ethnicity, the wealth of the state one is living in and many more (Cockerham 2007). Thus lifestyle is determined by much more than one’s own choice and based on an individual set of parameters that need to be taken into account in prevention projects. To give an example, the association between a healthy lifestyle and socio-economic status (SES) may, at least in parts, explain why the incidence of AD is higher in people with a low SES (Karp et al. 2004). In modernity, many different lifestyles have evolved that mean more to individuals than a random scheme of habits, as they allow one to position and identify oneself in society (Giddens 1991) and are expressions of world-views, individuality, and social status. This pluralism of lifestyles might counteract the strategies to randomize groups to standardized lifestyle interventions, simultaneously challenging public health endeavors to promote standardized behaviors.

Future Directions

We have introduced important components of a prevention program of AD, the components of which comprise avoidance of toxins, nutrition, culture of consciousness, exercise, and the cultivation of wholesome social relationships (see Table 12.1). However, rather than prescribing a single lifestyle for everyone, we would advocate individual titration and adaptation through a counseling process, which is normally more effective than just teaching or prescribing lifestyle changes (Appel et al. 2011). Lifestyle interventions have, in general, produced rather disappointing results in the field of cardiovascular and diabetes prevention (Angermayr et al. 2010; Ebrahim et al. 2011). We suppose that this is due to the fact that such programs normally try to produce a one-fit-all prescription. But lifestyles, being the expression of individual choices, predilections, and perhaps even genetic diversity, are as individual as people's faces. Thus the challenge will be to develop individualized programs that, via coaching, perhaps over the internet, will help individuals to adapt their personal lifestyle to become more wholesome, healthy, and yet in consonance with their personal choices. For instance, a reduction of carbohydrate intake can be achieved in various ways: one can eat less in one meal; one can eat less meals; one can eat normally over a period and then instal a short period of fasting; one can drop certain types of carbohydrates and replace them with other types; some of the calories normally ingested through carbohydrates can be replaced by other sources. A multitude of options exists, but in order to make a lifestyle change and choice durable, the choices need to be heartfelt, consciously chosen and practical. To quote another example: It is likely that a good provision with omega-3 PUFAs is an essential element of a good preventive diet. This can be achieved through regular consumption of fish, about twice a week. But what about people who do not like fish, or strict vegetarians? In these cases, they could then opt for supplements from algae, or change from the oils they are using to flax oil and walnut oil. They could prefer certain types of cheeses over others. Alternatively, people could just reduce omega-6 intake in order to lower the omega-6/omega-3 ratio. Only individual experimentation in conjunction with informed counseling can help.

Perhaps one of the first steps would be to find out what certain parts of the population are willing to try and to do. Implementation studies with a strong qualitative methodological backbone—focus groups, interviews, observational studies with documentation of behavior—are required to establish this. Counseling, either through personal contact or an interactive expert system, would be needed (Appel et al. 2011).

Another way of testing the potential benefit of such a program would be to use it, perhaps in a stronger "dose", also as a treatment program for people with mild cognitive impairment and to observe whether one can change conversion rates or cognitive decline. It is plausible to assume that if our, or other, programs and their components are useful in prevention, they should also be effective in treating very early symptoms of cognitive decline.

At any rate, we suggest that it is time to start researching lifestyle components as elements to prevent and, potentially, even treat dementia and cognitive decline. Most of the components we have mentioned—avoidance of smoking

Table 12.1 Substances and actions implicated in the prevention of AD, the main sources, and actions to take

Substance implicated	Main sources	Action	Evidence
Inorganic mercury	Dental amalgams, energy saving light bulbs, old thermometers	Avoid, carefully fade out	Mutter et al. (2010)
Organic mercury	Fish	Choose fish wisely, avoid fish that are known to contain more mercury, such as tuna and swordfish	Levenson and Axelrad (2006), Levitan et al. (2009)
Lead	Pipes, gasoline	Avoid and refurbish	Loef et al. (2011)
Aluminum	Cooking pots	Replace	Flaten (2001)
Iron	Supplements, red meats	Drop supplement, restrict red meat intake in people that are not at risk of a deficiency	Loef and Walach (2012a)
Copper	Supplements, pipes, oyster	Drop supplement, replace pipes	Loef and Walach (2012a)
Antioxidants	Green, leafy, and colored vegetables and ripe fruit, green tea, red wine, seeds such as mustard and almonds	Increase intake, prefer ripe and fresh produce, in times of allostatic overload consider whole-extract supplements	Devore et al. (2010), Loef and Walach (2012c)
Omega-3 PUFAs; Omega-3 to 6 ratio	Fatty fish, algae, and dark green herbs, flax oil, walnut (oil), almonds, granola oil	Increase intake, only in specific cases: consider supplements;	Issa et al. (2006), Lim et al. (2006), Fotuhi et al. (2009)
Omega-6 PUFAs; Omega-3 to 6 ratio	Animal fats, milk products unless from free range, plant oils (olive, sunflower, peanut, thistle, corn)	Decrease intake	(Loef and Walach 2012)
Carbohydrates and refined sugars	White and refined flour and baking, sugar and soft drinks	Avoid and replace with wholemeal wheat products, increase fat intake and reduce carbohydrates, drop the occasional meal, and increase fasting periods	Fontana and Klein (2007)

(continued)

Table 12.1 (continued)

Substance implicated	Main sources	Action	Evidence
Selenium	Wheat, fish, Brazil nuts	If mercury load is anticipated or present, supplement, else watch intake	Loef et al. (2011)
Folate and Vitamin B12	All leafy vegetables, wheat and milk, nuts, liver	If homocysteine is high, supplement	Oulhaj et al. (2009, van Dam and van Gool (2009)
Culture of consciousness	Meditation, mindfulness	Start learning and practicing regularly	(Pagnoni and Cekic 2007)
Exercise	Sports activities, biking, hiking, walking	At least 150 min per week of moderate to intensive activity	Hamer and Chida (2009), Graff-Radford (2011)
Social inclusion	Close relationships	Foster supportive relationships	Saczynski et al. (2006)
Overweight		Target a BMI of 18.5–25	Anstey et al. (2011), Siervo et al. (2011)

and the toxins mercury, lead, aluminum, a healthy diet; meditation and a culture of consciousness, as well as exercise and inclusive social relationships—have at least some evidence to support them, and those that have no direct evidence for them, such as meditation or inclusive social relationships, have some compelling indirect evidence that recommends them. Although we have here treated such lifestyle changes as preventive measures against AD and cognitive decline, they are rather generic. This we consider a strength rather than a weakness, as they are very likely preventive against quite a few other chronic diseases, such as cardiovascular disease, cancer, metabolic syndrome, and diabetes (Loef and Walach 2012f). In order to increase the adherence to a healthy lifestyle, it may therefore be of general interest to better understand the dependence of health behaviors on its multiple determinants. We suggest that research is directed toward this goal.

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Highlights

- Alzheimer's Disease, and indeed dementias, are complex diseases with no single causal mechanism that might serve as a therapeutic target. They start much earlier in life before any clinical sign are visible.
- This makes lifestyle, behavioral, as well as environmental factors potential multiple causes and possible access routes to public health measures, prevention, and perhaps also treatment at early stages.
- Among the most important factors are the avoidance of neurotoxins such as aluminum, mercury, lead; the provision with essential nutrients such as selenium, antioxidants, and a good balance of omega-3 to omega-6 essential fatty acids of 1:4 to 1:1; reduction in calorie intake; exercise; a culture of consciousness, such as meditation and active stress reduction techniques; participatory social structures.
- Important public health measures could be redistributing research efforts into studying how lifestyle, as an expression of lived individuality, could be molded through education and coaching to become more wholesome, and how such lifestyle decisions might impact on future prevalence of disease. Public education measures should provide the necessary information.

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Chapter 13
Social Determinants of Self-Regulation Development

Ezequiel M. Galarce and Ichiro Kawachi

Introduction

A healthy lifestyle is essential to a long and disease-free life. According to one estimate, over half of all premature deaths in the United States are due to poor personal choices—smoking, bad diet, sedentarism, dangerous driving, and risky sex (Keeney 2008). Opting for the healthiest behavior, however, is rarely an easy feat. Good intentions cannot influence health if a person is not able to continuously incorporate them into his/her lifestyle. Most people commonly experience a tension between what they intend to do to stay healthy and their actual behaviors. Eating a pastry instead of a slice of whole wheat bread, watching television instead of going out for a run, are often much more tempting than their healthier alternatives. For this reason, intending to do the right thing does not always translate seamlessly to being able to act upon such intentions.

Health decisions are influenced by internal states and environmental conditions. Every living organism engages in a determined behavior by virtue of unconditioned chemical processes and through associative learning. In this way, a thirsty animal will approach a river guided by the sound and smell of water. However, if the same animal were to catch a whiff of a nearby predator, it may decide to postpone drinking water to maximize its chances of survival. Competing demands such as these are ubiquitous in the animal and human world. In the case of the thirsty animal, survival depends on it being able to suspend the natural tendency to quench thirst until the threat is no longer active. Such postponement requires self-regulatory control over behavior.

Modern societies and their technological advances present us with an unprecedented array of choices that range from food and clothing to communications

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and entertainment. Many of these choices have helped us live longer and healthier lives. Others, such as calorie-dense foods and their accompanying omnipresent marketing efforts, may prevent us from achieving our health goals. How can a simple burger or a croissant derail us from important long-term health goals? Behavioral economists have elegantly demonstrated that most animals—including humans—display a heavy preference for immediate over long-term rewards.

How do people overcome their innate tendency to favor the here and now? Self-regulation is part of the solution. The ability to control our impulses and to delay gratification develops across the life course. This development influences most spheres of life, from health habits to professional and interpersonal success. Successful development of self-regulation partly depends on socioeconomic status and family processes. An increasing body of evidence is unveiling the association between early adversity and deficits in self-regulation development.

We argue that the relationship between adversity and self-regulation development is one pathway through which social inequalities arise in health behaviors and health outcomes (Sheffer et al. 2012; Stringhini et al. 2010). The first part of this chapter describes the role of self-regulation in health outcomes and how it develops under normal conditions. The second half addresses the influence of social determinants on such development.

Self-Regulation, Executive Processes, and Health

Self-Regulation

Self-regulation refers to the capacity to control behavior, as well as attentional and thought processes. Self-regulation is commonly equated to self-control.[1] In this sense, self-regulation also refers to the ability to choose a large delayed reward over an immediate but smaller reward (Barkley 2001; Dougherty et al. 2005). Thus, the capacity to delay gratification and inhibit behavioral impulses is an essential component of self-regulation (Mischel et al. 1989). This dimension can be understood from an energy standpoint. We have a limited capacity to regulate our behavior and this capacity can be depleted after continuous use to then be replenished (Baumeister 2002). Therefore, the capacity to inhibit prepotent responses varies intra- and inter-individually (i.e., state or trait) and can be modulated by surrounding contextual demands.

Inhibition—or behavioral omission—is rarely sufficient to prevent people from acting impulsively. Successful self-regulation also requires control at the

[1] Different dimensions of self-regulation have been examined over time under different terms: willpower (Metcalfe and Mischel 1999), hyperbolic discounting (Loewenstein and Elster 1992), grit (Duckworth et al. 2007), effortful control (Kochanska et al. 2000), self-control (Baumeister 2002), time preference (Fishburn and Rubinstein 1982), etc.

attentional level (Sethi et al. 2000). When in the presence of a tempting reward, the chances of opting for a delayed reward increases when attention can be displaced from the tempting item to the larger delayed reward. This process, in turn, requires the capacity to recall and maintain the long-term goal in a conscious and active state. When encountering repeated immediate versus delayed reward situations a person may develop plans and strategies that work best to favor the latter and avoid further engaging in behaviors that have not proven successful in the past.

All these processes involved in self-regulation (inhibition, attentional control, working memory, monitoring, planning, and shifting responses) are also dimensions of what cognitive psychologists refer to as executive functions. The ultimate goal of self-regulation—and underlying executive functions—is to maximize long-term net outcomes for an individual (Barkley 2001).

Executive Functions

Executive functions are high-level cognitive processes that exert top–down control over lower level processing (Williams and Thayer 2009). Although there is general consensus that executive functions are goal-directed, there is not a general consensus regarding their conceptualization and operationalization (Duckworth and Kern 2011). It is generally accepted that executive functions cannot be reduced to a single process, but is rather a group of goal-directed processes. These include inhibition, cognitive flexibility—also known as attention shifting—and working memory (Davidson et al. 2006). These three functions are moderately correlated but are separable at the level of latent variables (Miyake et al. 2000). The supervisory role of executive functions is usually extended to planning, reasoning ability, problem-solving, and the integration of thought and action (Shallice and Burgess 1996).

Executive inhibition is of special interest to those who study health behaviors. As implied in the previous section, self-regulation is commonly equated with inhibition. But inhibition is only a dimension or prerequisite of self-regulation (Barkley 2001). Inhibition has been studied in three different roles: prepotent inhibition, sustained inhibition, and interference control (Barkley 1997; Nigg 2000). The first refers to the capacity to inhibit the occurrence of prepotent or automatic responses triggered by associative processes. The second allows for the interruption of an ineffective ongoing behavior. Lastly, interference control prevents the disruption caused by competing cues and responses (Verbeken et al. 2009).

Executive functions can also be categorized depending whether they exert control over cold or hot processes. The former refers to the processing of emotionally neutral information which tends to assign priority to long-term goals. By contrast, hot processes refer to those that arise during states of physiological arousal and favor short-term goals. The study of executive functions' control over cold processes focuses on rapid-decision paradigms, attentional control and higher- over lower-order processing dominance (Nigg 2000). The role of executive functions in

emotional and motivational processes is usually examined as it affects impulsivity and delayed gratification (Dougherty et al. 2003; Hongwanishkul et al. 2005; Nichols and Waschbusch 2004)

Self-Regulation and Health Outcomes

Self-regulation has been associated with a myriad of health outcomes, behaviors, and social consequences. Prospective, cross-sectional, and experimental studies have confirmed a strong link between self-regulation—and its cognitive correlates—and health, quality of life, and life expectancy. For instance, studies have shown that self-control predicts psychiatric disorders and early mortality (Caspi et al. 1996; Kern and Friedman 2008). Others have revealed that low self-regulatory capacity may be followed by overeating, smoking, drunk driving, drug use, unsafe sex, non-compliance with medical treatments, and criminal behavior (Ayduk et al. 2000; Bogg and Roberts 2004; Caspi et al. 1994; Nigg et al. 2006; Tarter et al. 2003; White et al. 1994).

In a recent study, Moffitt et al. (2011) showed that self-regulation at age three predicts adult health problems at age 32, including cardiovascular, respiratory, dental, weight, airflow, and inflammatory status. This relationship remained significant even when accounting for intelligence (IQ), gender, and maternal socioeconomic status (SES). An earlier study found that childhood self-regulation capacity predicted substance use in adolescence, independently from parental characteristics (Nigg et al. 2006). More immediate effects of self-regulation have also been documented. For example, Graziano et al. (2010) found that self-regulatory capacity in toddlers predicted body mass index (BMI) at age 5.

The pathways through which self-regulation affects these outcomes is not entirely clear. However, there is a known link between self-regulation and general behavioral disinhibition (Bogg and Finn 2010). There is also evidence suggesting that children with a higher capacity for self-regulation have better attentional skills, can concentrate better and have more tolerance for frustration later in life than those with low self-regulatory capacity (Eigsti et al. 2006; Mischel et al. 1988).

Fewer studies have linked specific executive functions with health and behavior outcomes, but the evidence showing such associations is growing. For example, memory span has been linked to mortality in young adults, whereas performance on an IQ subtest that involves inhibition, working memory, processing speed, and sustained attention—i.e., digit symbol—has been found to predict mortality in older adults (Hall et al. 2009; Shipley et al. 2006). Working memory capacity has been associated with behavioral disinhibition which underlies various externalizing problems (Barkley 1997; Finn 2002; Hinson et al. 2003). Hall et al. (2008) showed that performance in a go/no-go task—a task that taps executive inhibitory capacity—predicts success in physical activity and dietary behavior in adults with intentions to improve those habits. More generally, executive functions have been found to play a critical role in mental and physical health, as well as in career and marriage success (Diamond and Lee 2011; Eakin et al. 2004).

Reaction time during cognitive tasks appears to be strongly associated with health outcomes and early mortality, as well. The speed with which a person reacts to a stimulus in a cognitive task heavily depends on executive processes related to sustained attention and task switching (Stuss et al. 2003; West et al. 2002; Yarkoni et al. 2009). Shipley (2006) analyzed data from 7,414 adult individuals and found that slower and more variable reaction times were related to an increased risk of all-cause mortality. This relationship was somewhat attenuated when controlling for SES, health behaviors, and health status. Reaction time has also been associated with hypertension, diabetes, pulmonary function, and low physical activity (Anstey et al. 2004; Hillman et al. 2006; Pavlik et al. 2005). Deary and Der (2005) have argued that reaction time is the key link between cognitive ability and health.

Analyses of cohort data across different countries have concluded that reaction time may mediate the association between intelligence and overall health as well as all-cause mortality. For example, a cohort study in Scotland revealed that IQ at 11 predicted survival at age 76 (Whalley and Deary 2001). Similar findings have been found in Denmark and Australia. These studies simultaneously controlled for sociodemographic factors (O'Toole and Stankov 1992; Osler et al. 2003).

Intelligence has also been linked to specific health behaviors and outcomes, such as hypertension, being overweight or obese, smoking and smoking cessation, and alcohol use (Batty et al. 2006, 2007a, b; Chandola et al. 2006; Gottfredson 2004; Gottfredson and Deary 2004; Starr et al. 2004; Taylor et al. 2003; White and Batty 2011). Other studies have linked intelligence with factors associated with midlife mortality, cardiovascular disease, unintentional injuries, suicide, and homicide risk (Batty et al. 2008; Gunnell et al. 2009; Hart et al. 2004; Hemmingsson et al. 2007; Lawlor et al. 2007; Osler et al. 2007).

Although studies have linked both executive functions and intelligence with health and health outcomes, there is yet no clear consensus as to what the association between executive functions and intelligence is (Arffa 2007). Friedman et al. (2006) found a strong correlation between working memory and the WAIS Full-Scale IQ and the Ravens Progressive Matrices. Others have found weaker correlations between executive tasks and tasks from the WAIS IQ test (Ardila et al. 2000). It has been suggested that the association between executive functions and intelligence may vary across the life course. There is also evidence that the relationship between these two measures is not linear but evident at extreme ranges of the intelligence continuum. For example, people with superior IQ also show high performance on oral fluency and inhibition tests (Parsons 1984).

The Development of Executive Functions

Executive functions are not a unitary cognitive process but a group or category or top–down processes. As such, different executive functions exhibit distinct developmental trajectories. Nonetheless, most executive processes show a marked improvement between 3 and 5 years of age. This corresponds with a significant

leap in the flexible use of rules (Hongwanishkul et al. 2005). As rules become more complex, and sometimes even contradictory, toddlers struggle to switch rules in response to new conditions (Jacques et al. 1999; Kirkham et al. 2003; Zelazo et al. 1996). For example, when 3-year-old children perform in the Dimensional Change Card Sort task (DCCS)—in which they are asked to sort cards according to their colors or shapes—they struggle to classify cards according to a new rule. Interestingly, they are aware and can verbalize such failure; a discrepancy that Zelazo et al. (1995) coined abulic dissociation (Munakata and Yerys 2001).

Increased control of attention, thought and action is a result of the acquisition of increasingly complex rule systems (Zelazo et al. 2003). Between the ages of 3 and 5, most children develop higher order rules (i.e., metacognition) which help them choose between two incompatible or conflicting rules. Task and rule shifting abilities continue to develop until the age of 15 when most children reach adult levels of performance (Kray et al. 2004). Metacognition is a critical process in inhibition tasks that require continuous choices between apparently contradictory rules (e.g., Stroop and Erisken Flankers task). Nonetheless, these types of task not only require a correct resolution between two contradictory rules but also resisting interference and withholding an incorrect prepotent response. Adult performance in inhibition tasks is not reached until adolescence (Huizinga et al. 2006). It should be noted that the aforementioned tasks require children to be able to remember the task rules. Working memory, or the ability to retain information in an accessible state, develops gradually throughout childhood and reaches its ceiling during early adulthood (Cowan 1998; Huizinga et al. 2006).

The abovementioned tasks tap mostly cool cognitive functions (Carlson 2003). By contrast, those stressing delay of gratification address motivational, incentive, and emotional processes. In Mischel's marshmallow test—a widely used measure of delayed gratification—children are asked to choose between an immediate reward (e.g., one marshmallow) versus a delayed reward with greater value (e.g., two marshmallows) (Mischel et al. 1989). Four-year-old children show a preference for the delayed reward, whereas 3-year olds generally choose the immediate one (Prencipe and Zelazo 2005). Similarly, in a gambling task the tendency shown by 3-year olds tend to choose cards with the higher rewards and risks shifts toward a more conservative strategy a year later (Kerr and Zelazo 2004). This transition reaches its ceiling at 5 years of age.

Social Determinants of Executive Function Development

There is ample evidence showing that poverty during childhood has a negative impact on the development of cognitive functions—including executive functions and intelligence—and on the neural mechanisms that support those functions (for a review Lipina and Colombo 2009). The effects of poverty and adversity on cognitive development have been studied from different perspectives, highlighting the roles of the pre- and postnatal environment, nutrition,

environmental toxins and hazards, home environment, neighborhood contexts, and parental SES (Evans 2004).

Poverty is often linked to prenatal exposure to toxic agents which have serious effects on cognitive functioning. For example, exposure to coal burning pollutants (i.e., polycyclic aromatic hydrocarbons) has been associated with delayed cognitive development, including language and intelligence up to 5 years of age (Edwards et al. 2010; Tang et al. 2008). These effects remained robust after controlling for tobacco exposure, gestational age, and maternal education. Similarly, prenatal exposure to polychlorinated biphenyls (PCBs) has been repeatedly associated with deficits in executive functions later in life (for a review Boucher et al. 2009). Prenatal exposure to even low concentrations of lead has been linked to low mental development scores during infancy and early childhood (Jedrychowski et al. 2009). A relatively new line of research is unveiling a robust association between parasite prevalence and intelligence, across US states and different countries (Eppig et al. 2010, 2011).

Even in the absence of such environmental hazards, poverty has been associated with delays and deficits in executive functioning development. Low SES status has severe developmental consequences in terms of mental development, both at a general level (e.g., intelligence) and at the level of more basic mental processes. Social, interpersonal, and resource characteristics associated with poverty have shown to have an adverse impact on attentional and inhibitory control, working memory, set shifting, and verbal processes in infants and children (e.g., D'Angiulli et al. 2008; Farah et al. 2008; Farah et al. 2006; Kishiyama et al. 2009).

Using the A-not-B task, which taps into infant attentional processes, cognitive control, and working memory, Lipina et al. (2005) found that infants from low socioeconomic backgrounds showed more errors on all such processes. Similar differences in attentional processes have also been reported in children 6 years of age (Mezzacappa 2004). Interestingly, in his study Mezzacappa also found that SES was associated with reaction times to different stimuli. It has been suggested that deficits in executive functions in this group stems from difficulties in discriminating relevant from irrelevant stimuli. This hypothesis has been confirmed by Stevens et al. (2009). These authors found that low SES children underperform in a selective auditory attention task. Moreover, using recordings of event-related potentials they showed that whereas children from more privileged backgrounds showed distinct neural responses in the prefrontal cortex to relevant and irrelevant cues, their low SES counterparts showed little discrimination. Differences in executive function have also been reported at older ages, with studies showing a performance gap up to middle school age (Farah et al. 2006; Noble et al. 2005).

Differences in executive function across the SES continuum have also been described in terms of delayed trajectories instead of mere deficits. These differences in developmental speed are already apparent at 6 months of life (Clearfield and Niman 2012). At this early stages, low SES infants show a 3-month delay in cognitive flexibility when compared to high-SES ones. This developmental gap is still apparent when children enter school (Bradley et al. 2001a, b; Brooks-Gunn and Duncan 1997; Duncan et al. 1998).

Mechanisms: Lack of Cognitive Stimulation and Stress

Lack of cognitive stimulation. Poverty affects cognitive development through various pathways, ranging from the quality of the social and home environment to parenting characteristics (NICHD 2005). Low socioeconomic contexts are commonly associated with low levels of cognitive stimulation, deficient emotional support, and high levels of unpredictability (e.g., Eamon 2005). When compared to transient states of economic instability, the strength of these associations increases in conditions of chronic financial hardship (Bolger et al. 1995; Korenman et al. 1995a, b; Linver et al. 2002; McLeod and Nonnemaker 2000; McLeod and Shanahan 1993).

During the first years of life, this micro-context (i.e., home or child-care facility) in which an infant develops has a critical influence on his/her mental development (Duncan 2003). School-age children also depend heavily on alternative sources of stimulation (Bradley et al. 2001a, b). Differences in stimulation between low income and middle income homes are sometimes dramatic. An influential study by Heart and Risley (1995) showed that children in high SES families are exposed to 2,153 words per hour. In contrast, those in welfare families only hear 616 words per hour. By the age of three, these differences amount to a 30 million word gap. There is evidence suggesting, however, that the conditions of the home environment improve when families move out of poverty (Garrett et al. 1994; Votruba-Drzal 2003).

The association between income and development is not linear. This relationship is much more robust on the low tail of the income distribution than that at the upper end (Bradley and Corwyn 2002). This relationship may be partly explained by the fact that income differences at the low end of the spectrum predict how cognitively stimulating a home environment is, whereas this relationship does not exist in high SES homes (Dearing et al. 2001). This nonlinearity is similar to the relationship between the relative influence of SES and genetics on intelligence (Turkheimer et al. 2003).

A longitudinal study of 2,457 British children showed how a privileged environment modulated the developmental cognitive trajectory of those how scored poorly at 22 months. By the time they were 10 years old, children of educated or wealthy parents caught up with those who scored on the upper ranges. In contrast, those who scored poorly at 22 months from low SES backgrounds never caught up. Moreover, within the low SES group the performance of those who initially had high scores declined (Feinstein 2003). This study provides evidence that cognitive ability is not static but demonstrates plasticity based on the home and social environment. These results are consistent with those of Danziger and Stern (1990) who showed that, when holding SES constant, single-parent families had negative effects on intelligence. Similarly, after analyzing data from the National Longitudinal Survey of Youth (NLSY) Korenman et al. (1995a, b) found that of the 10 to 15 point in IQ differential between high and low SES children, seven points could be attributed to the differences in the home environment. The detrimental consequences of a deprived home environment also extend to specific executive functions, such as attention and inhibitory control (Lengua et al. 2007; NICHD 2005).

Timing of adverse conditions, alongside with their duration, is another key aspect of the influence of poverty on cognitive development. There is evidence suggesting that chronic exposure to poverty during childhood affects development regardless of timing. Other studies show that poverty at the time of birth plays an important role in cognitive, language, and social competence development (Dearing et al. 2001). When comparing early (0–3 years old) versus late (4–9 years old) exposure to poverty, both groups show similar levels of cognitive deficits. Nonetheless, those who experienced poverty later also displayed externalizing behaviors (NICHD 2005). Through mediational analyses, the authors showed that these effects were produced through negative parenting patterns.

Stress. Lack of cognitive stimulation is only one side of the story of how poverty impacts development. Lack of parent support and living in an unpredictable environment can be especially stressful during childhood (Liston et al. 2009, 2006). Parents may inadvertently convey the stress of the broader social environment to their children (Conger and Donnellan 2007). Economic insecurity may also have a direct impact on children's development by way of presenting itself as an insecure and unpredictable environment. When a child is learning causal relationships between actions and consequences, between time of day and food, interruption of learned expectations may elicit negative forms of arousal.

Parents play an essential role in the early regulation of the hypothalamic–pituitary–adrenal (HPA) axis in infants (Gunnar and Donzella 2002). With the release of cortisol, the HPA-axis controls how the body reacts to stress. Cortisol is an important factor in the development of the brain, including areas associated with executive functions such as medial and dorsolateral prefrontal regions (Lupien et al. 2001). However, it has been suggested that chronically high levels of cortisol may impair the normal development of such areas (Lupien et al. 2009; Lyons et al. 2000).

Children from low SES backgrounds are more prone to display higher levels of basal cortisol (Lupien et al. 2001). Other studies found an association between cortisol and other biomarkers related to stress (e.g., heart rate and vagal tone) and self-regulatory skills in low SES children (Gunnar and Quevedo 2007). Cumulative exposure to sociodemographic, physical, and psychosocial risks during childhood has been recently associated with poor self-regulatory skills and increased BMI (Evans et al. 2012). Chronic stress during childhood is also associated with deficits in adult working memory (Evans and Schamberg 2009).

Acute stress may also play a role in the self-regulatory gap between low- and high-SES children. There is evidence that transient stress may lead to less efficient prefrontal cortex activity, resulting in decreased executive functioning (Arnsten 1998).

Discussion

The ability to control cognition and behavior while delaying gratification develops across the life course. The successful development of self-regulatory processes in turn affects subsequent trajectories of health, careers, and interpersonal

relationships. A growing body of evidence is unveiling the association between early adversity and deficits in self-regulation development. Poverty affects cognitive development through pathways ranging from the quality of the social and home environment to parenting characteristics. Moreover, biological risks may also affect child development prenatally. Cumulative exposures to environmental, biological, and psychosocial risks account for the divergent trajectories between high- and low-SES children.

Brain development is profoundly influenced by experience. Different categorization systems distinguish brain areas that depend on information during critical periods (e.g., sensory cortices) from those with sensitive periods (e.g., neocortical regions) (Bateson 1979; Cronly-Dillon and Perry 1979). A somewhat related taxonomy has been posed by Greenough et al. (1987) in which they differentiate experience-expectant from experience-dependent systems. The former refers to those areas that incorporate information common to all individuals and species (e.g., visual patterns, gravity, etc.). Experience-dependent regions process and store information that is unique to an individual, such as physical environment, vocabulary, and quality of childcare. Two differences become apparent between these two types of systems: (a) the type of information they depend on; (b) the window of opportunity during which information affects their development. What is common to both types of systems is that they are most plastic during the early stages of life (Lillard and Erisir 2011). The prefrontal cortex—critical to executive functions—is an experience-dependent region which exhibits a protracted developmental period that extends into adolescence (Sowell et al. 1999). Thus, its development can be affected by contextual factors—for better or worse—for a prolonged period of time. Moreover, the development of neurotransmitter regulation essential to prefrontal activity (i.e., GABA, glutamate, acetylcholine, norepinephrine, and dopamine) also exhibits a protracted developmental trajectory and thus may also be affected by early adversity (Pollak 2005).

Self-regulation is commonly conceived as the sole product of top–down processes. Nonetheless, the phenomenological output of self-regulation (e.g., attentional control, delayed gratification, impulsivity) is the joint outcome of executive control and other systems (i.e., bottom-up) that respond to internal and external cues through associative learning. In other words, the inhibitory role of executive functions implicitly includes the notion of another system/s attempting to act on spontaneous prepotent behavioral tendencies. These impulses are triggered by visceral states (e.g., hunger) and external cues (e.g., smell of fresh bread) (Strack and Deutsch 2004). The activation of these unconscious, automatic, rapid, and parallel processes is state-dependent (Nederkoorn et al. 2009). Associative networks are most reactive to cues when visceral states are salient (e.g., hungry). The influence of deprivation states over other systems is so pervasive that it can even affect visual perception (Radel and Clement-Guillotin in press). Health behavior is thus determined by the quantity and nature of external cues (e.g., junk food or tobacco advertisement exposure), internal states (e.g., hunger), the strength of associative processes (e.g., how strongly they are conditioned to respond to cues), and the capacity to inhibit those impulses while maintaining conscious long-term goals in an active state.

In this chapter, we have described how early experiences may affect executive processes associated with the maintenance of health behaviors. The science of the contextual influences on the development of such processes is growing at an accelerating pace. Little is known, however, about how early adversity affects the development of associative processes' reactivity to reward cues, or how present deprivation may modulate the relative weight of top–down versus bottom-up processing.

Furthermore, most current evidence linking early deprivation to developmental deficits or delays is correlational. Thus, causal relationships between context and cognitive development cannot yet be readily established. The data are however highly suggestive. Human—as well as other animal—experimental designs are needed to establish not only a causal direction but to refine the nature of those relationships. Not all aspects of early adversity are likely to affect cognitive processes in the same way. However, at this point we cannot determine the relative importance of stimulation, emotional support, or stress on the development of different self-regulatory processes.

Better understanding of such problems will allow for more optimal childcare, educational, and environmental interventions aimed at boosting self-regulation and narrowing the developmental gap between high- and low-SES children.

Highlights

1. Self-regulation is involved in the top–down control of attentional, behavioral, and motivational processes. Self-regulation is thus associated with health behavioral maintenance.
2. The development of self-regulatory processes is partly modulated by external influences, such as cognitive stimulation and stress.
3. Childhood poverty may affect self-regulation development through psychosocial mechanisms, as well as chemical and biological ones.
4. Further advancing our understanding of how early adversity affects self-regulation, and health behavioral maintenance, will contribute to the design of better public health interventions aimed at narrowing existing gaps in health between high and low socioeconomic groups.

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Part V
Exercise Neuroscience

Chapter 14
Physical Activity, Cardiorespiratory Fitness, and Cognition Across the Lifespan

Edward McAuley, Sean P. Mullen and Charles H. Hillman

Introduction

The demographic landscape of the United States is undergoing a transformative shift. As a nation, we are becoming older (Center for Disease Control and Prevention/ National Center for Health Statistics [CDC] 2009; Goulding et al. 2003), less active (Pleis and Lucas 2009), and more overweight/obese (CDC 2010). For example, the proportion of the population aged 65 years or older is projected to increase from nearly 35 million in 2000 to approximately 71 million in 2030 (CDC 2009; Goulding et al. 2003). The rapidity of this trend is even more pronounced in the segment of the population aged 80 years and older. Additionally, in spite of the well-documented benefits of regular physical activity, participation rates have either remained stagnant at alarmingly low levels, or have declined. Most recent estimates suggest that 35 % of adults aged 18 years and older engage in regular leisure-time activity, 32 % engage in some leisure time activity and approximately a third are inactive (Pleis and Lucas 2009). As one might predict, there is a consistent decline in activity with age with 44 % of those 75 years and older being inactive (Pleis and Lucas 2009). Paralleling these levels of inactivity, not surprisingly, are the national statistics associated with overweight and obesity. Obesity levels have steadily risen in adults 20 years and older from 19.5 % in 1997 to 34 % in 2007–2008 (CDC 2010) and these numbers are higher for Hispanic and African American adults. Such figures are not unique to the United States, with the United Kingdom having the highest rates of obesity (i.e., 22.1 % for men and 23.9 % for women) in the European Union (European Commission: Eurostat 2011). It is of considerable concern that these gradient increases are also demonstrated in children and adolescents.

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One of the more commonly associated outcomes of the aging process is cognitive decline, which is typically characterized by decrements in a variety of processes including aspects of memory, attention, and perception. These declines have been identified as a major risk age-associated diseases such as Alzheimer's Dementia (Wilson et al. 2002). Consequently, development of strategies to maintain or enhance cognitive function in later life is an important public health goal. Physical activity and exercise training have been targeted as behavioral modalities with the potential to preserve cognitive function and brain integrity and a considerable literature studying both animal and human models has evolved (for reviews see Hillman et al. 2008; McAuley et al. 2004; Thomas et al. 2012; Voss et al. 2011b). However, it is only over the last decade and a half that strong evidence for exercise effects on brain and cognition in humans has emerged. This is in large part due to better designed randomized controlled trials, availability of more sophisticated imaging technology, and greater specification as to which aspects of cognitive function appear to be more sensitive to exercise training.

In this chapter, we begin by reviewing the literature relative to physical activity, exercise training, and cardiorespiratory fitness associations with cognitive function, especially executive control, and brain structure and function in older adults. Given the declines in cognitive function that have been demonstrated beyond midlife (Willis and Schaie 2005), this represents the greatest proportion of the literature in this area. Next, we review studies of the physical activity and cognition relationship in children and adolescents. This rapidly expanding corpus of work has garnered considerable interest given its potential for understanding physical activity effects on academic achievement. Finally, we close the chapter with a brief overview of emerging areas of research and potential for future developments in the physical activity and cognition field.

Physical Activity and Cognition: Older Adults

Cognitive decline is in part, the result of normative age-related changes in brain structure and function (Drag and Bieliauskas 2010). Generally speaking, aging is associated with decreased brain volume and diminished executive control. The latter involve goal-directed processes such as the ability to retain information in the contents of working memory, focusing attention in the presence of distractors, inhibition of habitual responses, and the ability to switch perspectives or response mappings in a fluid and flexible manner. Such processes are implicated in everyday planning and decision-making, but are also associated with motor functioning (i.e., gait speed and balance (e.g., Coppin et al. 2006; Huh et al. 2011; Yogev Seligmann et al. 2008), and falls (Anstey et al. 2009). Some researchers have proposed that domain-specific deficits (e.g., memory, attention, and inhibition problems) underlie age-related decline, whereas others have suggested a generalized slowing in cognitive function (e.g., Salthouse 1996). Although the mechanisms

underlying the cognitive consequences of aging are still a source of debate, there is a growing consensus that cognitive vitality can be enhanced by leading a physically active lifestyle and particularly through enhancements in cardiorespiratory fitness. Aerobic fitness has been posited as potential mechanism responsible for cognitive benefits, given its association with enhanced cerebral blood-flow, reduced inflammation, and improved structural and functional connectivity among neural networks. Other mechanisms such as neurogenesis, synaptogenesis, and angiogenesis at the cellular level and increases in neurotransmitters (e.g., brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (igf-1) at the molecular level have also been hypothesized (Cotman et al. 2007; Hillman et al. 2008).

Physical Activity, Cardiorespiratory Fitness, and Cognition

A number of cross-sectional and population-based studies have suggested that physical activity is associated with a host of cognitive benefits. For example, in a 6–8 year follow-up of 5,925 older women, Yaffe et al. (2001) reported that those who walked more were less likely to demonstrate cognitive decline. In the Canadian Study of Health and Aging, Lindsay et al. (2002) found that physical activity, among other healthy lifestyle behaviors, was associated with lower risk of Alzheimer's disease. Similarly, Laurin et al. (2001) have reported physical activity levels to be inversely associated with cognitive declines and dementia. In another large sample of older adults ($N = 1{,}740$), Larson et al. (2006) found that those exercising ≥3 times per week had lower incidence rates of dementia, and older women from the Nurses' Health Study who were the most physically active (upper 20 %) had a 20 % lower risk of cognitive impairment relative to the least active (lowest 20 %) (Weuve et al. 2004). More specifically, Weuve et al. reported increased physical activity was associated with improved verbal fluency, memory, attention, and global cognition. Although data from these population studies are intriguing, randomized controlled exercise trials offer more compelling arguments relative to the physical activity and cognitive impairment relationship in late life.

Several randomized controlled trials have been designed to test the effects of changes in cardiorespiratory fitness on changes in executive control among older adults. In an early study, Kramer et al. (1999) observed selective benefits across task conditions requiring extensive amounts of executive control (i.e., inhibition, working memory, and mental flexibility) for participants in the aerobic exercise condition compared to a stretching and toning condition. That is, the observed benefits with aerobic exercise were not observed for more simple tasks that had smaller executive control components. In a meta-analysis of 18 randomized controlled exercise training trials with older adults, Colcombe and Kramer (2003) reported significant effects for exercise training interventions across a broad array of cognitive functions. However, the largest effect ($g = 0.68$) was demonstrated for those tasks or task components which required greater levels of executive function. A more recent meta-analysis by Smith et al. (2010) included a more contemporary literature review

and reported that the effect of exercise training on executive function was smaller ($g = 0.12$). Some of the ambiguity between meta-analyses may have resulted from the fact that Smith et al. included trials with adults aged 18 years and older, whereas Colcombe and Kramer (2003) only included studies with older adults. Other recent studies have corroborated the relationship between physical activity and executive function, as Baker et al. (2010) found improvements in executive control after a 6 months aerobic exercise intervention involving treadmills, elliptical trainers, and stationary bicycles; and Anderson-Hanley et al. (2012) showed that a 3-month "cybercycling" intervention (i.e., recumbent stationary ergometer with virtual reality [VR] display enabled) had more positive effects on executive functioning than traditional bicycling (VR-disabled). Together the findings indicate that physical exercise training has a beneficial influence upon executive functioning, but the robustness of the relationship requires continued investigation.

Cardiorespiratory Fitness and Brain Structure and Function

Technological advances (e.g., structural and functional magnetic resonance imaging [MRI]) have afforded scientists studying exercise effects on cognition the opportunity to examine whether the human brain's structure and function are affected by factors such as physical activity involvement, exercise training, and cardiorespiratory fitness (see Thomas et al. 2012; Voss et al. 2011a). However, a number of studies have reported both structural and functional aspects of the brain to be associated with physical activity participation and, particularly, cardiorespiratory fitness. For example, in an earlier multi-study publication, Colcombe et al. (2004) demonstrated that older, more fit adults had significantly greater activation in those cortical regions implicated in executive control (i.e., frontal, temporal, and parietal cortices) than a group of low fit adults. In addition, the low fit sample showed greater activation in the anterior cingulate cortex, an area thought to mediate aspects of behavioral conflict. In their second study, Colcombe et al. (2004) replicated these findings in a randomized controlled trial. Specifically, participants in a 6-month aerobic exercise condition showed greater inhibition and demonstrated greater plasticity than a non-aerobic exercise control condition. Rosano et al. (2010) have also reported improved functioning of key nodes in the executive control network in participants who remained active 2 years following the cessation of an exercise intervention with greater activation observed in the inferior frontal gyrus.

Additionally, participation in aerobic exercise training interventions has been associated with greater gray and white matter volume in the prefrontal cortex of older adults (Colcombe et al. 2003, 2006). Moreover, hippocampal and medial temporal lobe volumes have been reported as being larger in higher fit older adults (Erickson et al. 2009; Honea et al. 2009) and larger hippocampal volumes mediate improvements in spatial memory (Erickson et al. 2009). In a recent study, Erickson et al. (2011) reported that older adults who engaged in 12 months of supervised aerobic exercise (i.e., walking) had greater improvements in spatial working memory

and a 2 % increase in hippocampal volume, resulting in the reversal of age-related loss by 1–2 years. Importantly, hippocampal volume change has been shown to partially mediate the relationship between fitness change and spatial memory performance (Erickson et al. 2009) and is associated with greater serum levels of brain-derived neurotrophin factor (BDNF; Erickson et al. 2011). Other researchers have also shown relationships between exercise and cardiorespiratory fitness and whole brain and white matter regions (Burns et al. 2008; Marks et al. 2011). Overall, it would appear that, exercise serves a protective effect against volumetric declines associated with the aging process.

Finally, in an important extension of previous work examining exercise effects on the aging brain, Voss et al. (2010) reported that 12 months of aerobic and non-aerobic training were associated with greater functional connectivity in the default mode network (DMN), i.e., the brain regions activated during rest periods. Specifically, aerobic activity increased functional connectivity within the DMN and a frontal executive network, two brain networks central to brain dysfunction in aging. However, these effects in the walking condition were observed only after 12 months of training. The non-aerobic condition, which engaged in stretching and toning exercises, also showed increased functional connectivity in the DMN after 6 months and in a frontal parietal network after 12 months. These latter findings may be explained by the learning component of the non-aerobic activity, which required learning new routines and movements and possibly reflects an experience-dependent plasticity.

Intensity and Mode of Activity and Cognition

It is unclear as to the dose-response relationship between exercise training and cognitive benefits. Colcombe and Kramer's (2003) meta-analysis suggests that benefits are most likely attained if the exercise duration is at least 30+ minutes per session. More recently, a meta-analysis of acute exercise effects, Chang et al. (2012) confirmed that bouts of >20 min were associated with the greatest pre-exercise, during-exercise, and post-exercise effects on cognition, although the positive acute effects were small for older adults ($d = 0.18$). Chang et al. (2012) also found that low levels of fitness were associated with a negative effect on performance, which suggests at least in the short-term, that exercise can potentially drain cognitive resources among less fit or less active adults. Although the duration of exercise needed for cognitive benefits is relatively consistent, the literature is less clear about levels of intensity. Whereas several randomized controlled trials have involved aerobic exercise at moderate-to-vigorous intensities, Lautenschlager et al. (2008) found improvements in delayed recall after 6 months of moderate-intensity walking, which were maintained at the 6-month follow-up. Prospective studies also indicate that moderate-intensity walking is sufficient for reducing the likelihood of cognitive decline (Geda et al. 2010; Yaffe et al. 2001) and some of the more rigorously designed studies have used moderate intensity walking to good effect [e.g., (Colcombe et al. 2006; Erickson et al. 2011)].

The benefit of non-aerobic exercise modalities (e.g., strength and flexibility training) in cognitive functioning has been given less attention, although the findings of Voss et al. (2010) would suggest the learning aspects of such activities have potential for enhanced plasticity in the aging brain. Such work is supported by a wealth of animal literature on the effects of environmental enrichment on brain structure and function (e.g., Greenough and Black 1992). Indeed, in a recent randomized controlled study, Anderson-Hanley et al. (2010), showed that 4 weeks of lower body strength training improved executive control. There have been a number of studies examining resistance training effects on cognition but the literature is equivocal, mainly reliant on studies with small samples sizes and comprised of relatively short interventions. In larger studies, Kimura et al. (2010) failed to find any effect of 12 weeks of resistance training on executive function and Lachman et al. (2006) reported an overall effect of a home-based strength training intervention on memory in a large sample of older adults. However, higher resistance was associated with improved memory suggesting that intensity of the exercise stimulus may be important. This latter point has been supported by one of the few randomized trials of resistance training that has incorporated an intervention of greater duration. In a 12-month intervention study, Liu-Ambrose et al. (2010) reported that progressive resistance training was associated with improved conflict resolution and selective attention. Importantly, these gains in cognitive function were associated with improved gait speed, a marker for reductions in morbidity and mortality.

Concluding Remarks

Although many studies have demonstrated cognitive benefits as a function of physical activity, there have been some that show inconsistent or null effects. For example, van Uffelen et al. (2008) reported no effect of a 12-month supervised aerobic walking intervention on memory and executive functioning; however, they did report modest positive effects among a subgroup of participants with the best compliance to the intervention, indicating that those who have less compliant may have been physically active at a rate below that necessary for changes in cognition. Sturman et al. (2005) also found no relationship between physical activity and cognitive functioning after adjusting for depression, vascular disease, likelihood of preclinical dementia, and participation in cognitively stimulating activities. Interestingly, the van Uffelen et al. (2008) review suggests that exercise may be more beneficial in those who have already experienced some cognitive decline, as a greater proportion of studies showing positive cognitive effects were based on impaired samples. However, findings reported by Erickson et al. (2011) were based on healthy, community-dwelling samples. In Smith et al. (2010) meta-analysis, aerobic exercise interventions showed positive effects on attention, processing speed, executive control, and declarative memory, but inconsistent effects on working memory. Inconsistencies may point to methodological differences across studies. Accordingly, there remains the need to systematically evaluate dose–response

effects of exercise training on cognitive function and to further examine the effects of exercise alone versus engagement in activities that involve simulating activity and the learning of new skills. For this reason and other methodological issues, some scientists remain skeptical that *physical exercise* is responsible for changes in cognitive functioning (Miller et al. 2012) rather than changes in depression and social or cognitive stimulation brought about by exercise. However, given the wealth of data in human and non-human animal models that has provided considerable support for a primary relationship of physical activity on cognitive and brain health, it is much more likely that direct relationships of physical exercise on cognition not only exist, but also evolved to meet the demands of everyday life (Vaynman and Gomez-Pinilla 2006).

Physical Activity and Cognition in Children

Unlike the study of physical activity and cognitive aging, which has enjoyed several decades of research advances, the study of physical activity and cognitive development is a more recent focus of researchers and practitioners. Much of this concern stems from epidemiological findings indicating that children are less active and more obese than ever before (Ogden et al. 2012), with recent data suggesting that, for the first time in U.S. history, the current generation of children may have shorter lives than previous generations (Flegal et al. 2002). The study of children is also intriguing for other reasons. That is, early experiences shape behavior and its neural underpinnings. For example, Greenough and his colleagues (Black and Greenough 1986; Greenough and Black 1992) distinguish between experience-expectant and experience-dependent influences upon neural development. Experience-expectant influences refer to situations or environments that are typical to a species, and are required for normal organization of the nervous system to occur. Experience-dependent influences refer to non-typical (i.e., idiosyncratic) interactions with the environment that stimulate new brain growth and/or the sculpting of neural networks to support these unique experiences. In this manner, experience-dependent processes shape the individual's adaptations to the environment on neural, and consequently behavioral, levels. Idiosyncratic experiences brought about by socioeconomic status and quality of education are experience-dependent factors, as is physical activity, which varies considerably during the developmental years, and has implications for cognitive and brain health.

Academic Achievement

Recent studies have indicated that physical activity and aerobic fitness are associated with academic achievement in children (Hillman et al. 2008), suggesting that these factors may provide experience-dependent influences upon neural

networks supporting cognitive and brain health. Both cross-sectional (see CDC 2010; Tomporowski et al. 2008) for reviews) and longitudinal (Donnelly et al. 2009; Dwyer et al. 1983; Sallis et al. 1999) study designs have found that time spent being physically active did not detract from educational outcomes, and in some cases may be associated with improved scholastic performance. That is, several studies have observed a positive relationship of physical activity or aerobic fitness with academic achievement (Castelli et al. 2007; Chomitz et al. 2009; Coe et al. 2006; Grissom 2005). Alternatively, other studies have observed no relation between physical activity and academic achievement (Dwyer et al. 1983), indicating that although increased participation in physical activity did not lead to higher academic achievement, it also did not detract from it. Regardless, such a pattern of findings suggest that greater amounts of physical activity may be beneficial to physical health, at no cost to educational attainment, and serve to promote physical activity during and beyond the scholastic environment for all children.

Cardiorespiratory Fitness and Brain Structure

More recently, research has been aimed at understanding the cognitive processes and neural structures that underlie the relation of physical activity/aerobic fitness to scholastic performance. Cross-sectional studies have identified brain structures that are influenced by aerobic fitness. For example, Chaddock et al. (2010) observed that specific regions of the basal ganglia (i.e., regions of the dorsal striatum: caudate nucleus, putamen, globus pallidus), which support cognitive control, are enlarged in higher fit children, while other areas of the basal ganglia (i.e., nucleus accumbens), which support affect and reward, did not differ. Further, higher fit children exhibited superior performance during a task requiring inhibitory control, and these behavioral findings were mediated by basal ganglia volume. As such, the findings suggest that fitness is related to the volume of specific regions of the basal ganglia, which support behavioral interactions during tasks that require executive control.

In addition, Chaddock and her colleagues (Chaddock et al. 2010, 2011) conducted two studies to investigate the relation of fitness to relational memory in preadolescent children. Relational memory is dependent upon the hippocampus, and refers to the ability to bind arbitrary items into cohesive entities and form lasting memories of these new associations (Cohen and Eichenbaum 1993). Chaddock et al. (2011) demonstrated that higher fit children performed better on a relational memory task, which required the binding of faces to houses, while no such relationship was observed for an item memory task, which requires a lasting representation of a single unit and is thought to be mediated by the medial temporal lobe adjacent to the hippocampus (Eichenbaum and Cohen 2001). In a follow-up investigation, Chaddock et al. (2010) replicated the selective benefit of fitness on relational memory and further observed that hippocampal volume was not only enlarged in higher fit children, but that the volume mediated the selective

relationship between fitness and relational memory performance. Such findings demonstrating fitness related benefits to hippocampal-dependent learning and memory are supported by a wealth of non-human animal models (e.g., Cotman and Berchtold 2002), and suggest that physical activity may have a selective and disproportionate influence upon specific cognitive functions; rather than a global influence on cognitive and brain health.

Cardiorespiratory Fitness and Brain Function

In addition to examining the association of fitness with brain structure in children, several studies have observed influences upon brain function as well. For instance, event-related brain potentials (ERPs) have proven to be useful in understanding covert aspects of cognitive function that occur between stimulus engagement and response selection, which are related to aerobic fitness. A series of studies conducted in preadolescent children has suggested that higher fitness is related to specific neuroelectric components. Such an approach affords inference into which aspects of cognition that occur between stimulus engagement and response execution may be influenced by fitness. Specifically, extensive research on the P3 component (a neuroelectric component concerned with the allocation of attentional resources in the service of updating working memory operations) has demonstrated larger amplitude in higher, relative to lower, fit children (Hillman et al. 2009, 2005; Pontifex et al. 2011, but see Hillman et al. 2008, for review). In addition, shorter P3 latency has been observed for higher fit children, indicating faster cognitive processing speed. As such, these findings indicate that higher fitness is associated with greater attentional capture and faster processing of the stimulus environment.

Other studies have observed that fitness also modulates the error-related negativity potential, a neuroelectric component concerned with action monitoring (Hillman et al. 2009). Specifically, smaller ERN amplitude has been demonstrated in higher, relative to lower, fit children during tasks that require less executive control (Pontifex et al. 2011). However, during tasks that require greater amounts of cognitive control, higher fit children exhibit larger ERN amplitude, while lower fit children exhibit no change in ERN (Pontifex et al. 2011). Combined with the P3 data, such findings suggest that higher fit individuals may be more effective in capturing information in the environment, and thus, rely less upon action monitoring strategies to ensure correct performance relative to lower fit children. However, under task conditions requiring greater amounts of executive control, higher fit children appear to flexibly upregulate action monitoring to ensure both effective stimulus capture and correct action. Such a cognitive strategy is not only flexible, but appears necessary for high level performance, as higher fit children exhibit more accurate behavior when compared to their lower fit peers during tasks requiring variable amounts of executive control (Pontifex et al. 2011).

Other research has employed fMRI to assess brain function during executive control tasks in higher and lower fit children (Voss et al. 2011a, b). Findings

have indicated that higher and lower fit preadolescent children exhibit differential patterns of activation across three clusters, suggesting a different strategy during performance of an executive control task requiring variable amounts of inhibition. Specifically, lower fit children had more activation across neural structures involved in response inhibition (e.g., pre- and post-central gyus, supplementary motor area, dorsal anterior cingulate gyrus, left superior parietal lobule), prolonged task maintenance (e.g., cingulo-opercular network), and top–down control (e.g., left anterior prefrontal cortex, middle frontal gyrus, frontal pole). That is, higher fit children exhibited more activation during task conditions requiring lesser amounts of control, with little upregulation of control (i.e., little modulation of activation) during tasks requiring greater amounts of executive control than did their less fit counterparts. This pattern of results suggests that higher fit children may execute a strategy that involves proactive control, while lower fit children use a more reactive control strategy (Pontifex et al. 2011; Voss et al. 2011a, but see Braver et al. 2009). Such differences in control strategy have implications for task performance, as higher fit children demonstrated greater inhibitory control between task conditions.

Concluding Remarks

Finally, to date, only two studies have employed randomized control designs to assess physical activity influences on neurocognitive function in children (Davis et al. 2011; Kamijo et al. 2009). These trials employed fMRI (Davis et al. 2011) and ERP (Kamijo et al. 2009) techniques and observed increased executive control following a physical activity intervention relative to baseline and a non-active control group. Across studies, the finding indicated that increased physical activity levels were associated with better executive control across tasks requiring inhibition (Davis et al. 2011) and working memory (Kamijo et al. 2011); processes that are at the core of executive control. Collectively, findings in children support physical activity as a potential means for promoting cognitive and brain health, which has implications for scholastic achievement during development and effective functioning across the lifespan.

Emerging Trends and Future Directions

The evidence to indicate that exercise training and cardiorespiratory fitness prevent declines in cognitive function and hippocampal volume and are associated with more efficient use of the brain in older adults has grown dramatically in the last decade. This, coupled with an exciting, emergent literature in children is suggestive of yet another important health benefit of physical activity across the lifespan. In this concluding section to the chapter, we briefly consider some emerging

trends in this literature and several important directions that are worth greater scientific scrutiny.

For example, cognitive training approaches which teach strategies that help encode and retrieve information (e.g., Gross and Rebok 2011) have been shown to be efficacious in maintaining and improving cognitive and functional abilities in daily life (e.g., Hertzog et al. 2009). Whether cognitive training combined with exercise has a synergistic effect on cognitive functioning and brain health has yet to be empirically tested (Anderson-Hanley et al. 2012; Fabre et al. 2002; Jak 2011). Additionally, whether cognitive training may also have transfer effects on the self-regulation of physical activity behavior is an intriguing area of inquiry. For example, Hall and his colleagues (Hall et al. 2008, 2012; also see this volume, Chap. 10) found that executive function, as measured by the Go/No-Go task, predicted short-term exercise participation in young adults. In a randomized controlled physical activity trial of older adults, McAuley et al. (2011) demonstrated that aspects of baseline executive function (i.e., multi-tasking and inhibition) were significant predictors of subsequent long-term exercise adherence through the mediation of self-efficacy. This literature further extends the notion of cognitive plasticity, "near and far transfer effects" (Barnett and Ceci 2002), and the reciprocal relationship between physical activity and cognition. Moreover, these studies serve as evidence for the successful bridging of motivational and cognitive elements of social cognitive theories.

Whereas there is an increasing literature relevant to exercise training effects on cognitive outcomes and brain structure, it is unclear at this time whether such improvement translates to meaningful, clinically important outcomes associated with the aging process. For example, is enhanced cognitive function associated with improved balance and therefore implicated in reducing the incidence of falling? Some evidence indicates that improved cognitive function from exercise training, specifically strength training, is associated with mobility; an important health outcome (Liu-Ambrose et al. 2010). Another important clinical outcome for older adults is memory complaints. The prevalence of memory problems in older adults range from 25 to 60 % (De Jager et al. 2005; Jonker et al. 2000), understanding the biological, behavioral, and physiological factors that may influence these problems is an important public health issue. Szabo et al. (2011) demonstrated that cardiorespiratory fitness was associated with fewer memory problems and that this relationship was mediated by hippocampal volume and spatial working memory. Although cross-sectional, if such a relationship holds following exercise training, this would have important health and societal implications.

Whereas the effects of exercise training on cognition and brain health are quite impressive, as noted previously, there remain studies that report null or very small positive effects. Thus, it will become more important for scientists to begin to examine the role that individual differences may play in exercise effects. For example, factors such as genetics, physiological status, disease status, lifestyle, and personality may be implicated in which individuals successfully respond to exercise training and those who do not. Importantly, even the existing larger exercise trials are insufficiently powered to conduct such moderator analyses. Future

trials should take this into account when designing interventions that propose to examine potential moderating and mediating effects.

Voss et al. (2011b) have recently called for multi-modal approaches to brain imaging across the lifespan. In addition to neuroelectric and hemodynamic approaches to the assessment of brain function, they advocate the use of measures that better assess blood flow and volume such as arterial spin labeling, which may allow scientists to more fully explore the mechanisms underlying the exercise-training effect on brain and cognition. Further, Voss et al. recommend incorporating approaches that better assess white matter integrity such as diffusion tensor images. The combination of these contemporary methods with those methods more frequently applied would make for a powerful technological arsenal for understanding exercise and brain health.

Although there is a considerable body of work relative to physical activity and cognition in older adults, research on physical activity and the developing brain has only recently begun. As such, there are a number of future directions that are relevant to brain health and scholastic achievement, which have yet to be explored. At the level of basic science, neuroimaging findings have been promising in linking fitness to changes in brain structure and function in both cortical and subcortical structures. However, considerably more work remains to fully detail the relationship of fitness to brain health. More imaging studies are needed to better understand the general versus selective nature of fitness effects on brain structure and function during development, and to provide a foundation for the application of such findings to everyday life. Additionally, there remains a need for well-controlled, randomized trials to replicate the findings that have begun to appear in the literature based upon cross-sectional and observational studies. Accordingly, translational research is needed that moves beyond the physical activity and neuroimaging relationship to examine functional aspects of school including classroom experiences, play, and socialization. That is, an understanding of how physical activity behaviors influence attention, cognition, and memory has implications for not only scholastic achievement, but also vocational success, and effective functioning throughout the lifespan. Finally, future research must consider other lifestyle factors such as diet, nutrition, and body composition, as preliminary evidence suggests that these factors also are related to brain and cognitive health.

Concluding Remarks

It is clear that great strides have been made in the field of physical activity, exercise training, and brain and cognition. However, it is also apparent that much remains to be accomplished. Exciting developments and advances across the lifespan are emerging at an exponential rate, new methodologies are rapidly developing, and there are an increasing number of randomized controlled trials. Scientists are encouraged to build on this foundation to stave off cognitive decline, enhance cognitive and neural benefits, and improve quality of life across the lifespan.

In this chapter, we have presented findings that have important implications for public health outcomes as broad as falls prevention and quality of life in older adults and potential educational advantages in children. As such, we would argue that such evidence should further reinforce public health policies to keep seniors and children physically active by adding brain health to the list of demonstrated benefits of a physically active lifestyle.

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Highlights

- Physical activity is associated with cognitive and brain health across the lifespan.
- Physical activity effects on cognition appear to be selectively stronger for tasks that require extensive amounts of executive control.
- Public health policies to keep seniors and children physically active should include brain health among the demonstrated benefits of a physically active lifestyle.

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Chapter 15
Brain Glycogen Decrease and Supercompensation with Prolonged Exhaustive Exercise

Takashi Matsui and Hideaki Soya

Exercise activates the brain as well as skeletal muscles, and increases demand of energy and oxygen in the brain. Although the energy source for the brain should be exclusively carbohydrates, responses, and adaptations of carbohydrate metabolism in the brain are still unclear.

In skeletal muscles, exhaustive exercise results in glycogen depletion, but glycogen returns to above basal levels (*supercompensation*) approximately 24 h after cessation of exercise (Bergstrom and Hultman 1966). It is well-known that an adaptation to meet the increased energy demand in skeletal muscle with exercise training is based on glycogen supercompensation following exercise (James and Kraegen 1984). On the other hand, brain glycogen, which localizes in astrocytes, is an important energy source for neurons (Brown 2004). Astrocytic glycogen is degraded into lactate to provide fuel for neurons during sleep deprivation, hypoglycemia and memory formation (Kong et al. 2002; Herzog et al. 2008; Suzuki et al. 2011), suggesting a role for glycogen in energy provision during sustained neuronal activity. Exercise also increases neuronal activity and creates an energy demand in the brain (Vissing et al. 1996; Ohiwa et al. 2007; Soya et al. 2007). Although untested, it is hypothesized that glycogen decrease and supercompensation occur in the brain, as well as in skeletal muscle, following exhaustive exercise.

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Energy Sources for the Brain: Astrocyte–Neuron Lactate Shuttle

The astrocyte–neuron lactate–shuttle hypothesis posits that lactate released from astrocytes into the extracellular space is metabolized by neurons (Pellerin and Magistretti 1994) (Fig. 1). Until recently, only blood-borne glucose was considered as an energy source for the brain. However, current studies have shown that when there is neuronal activation, lactate is released from astrocytes and the neurons consume it predominantly for energy. Furthermore, culture experiments have shown that glycogen localized in astrocytes is degraded into lactate by excitatory neurotransmitters such as noradrenaline and serotonin, and can contribute to the release of lactate from astrocytes to neurons through glycolysis (Brown 2004).

Brain Glycogen Detection by Using Microwave Irradiation

Not so long ago, it was believed that the brain glycogen levels were so low that they would not play a significant role in cerebral metabolism during several physiological stimulations including exercise. Furthermore, there are technical difficulties

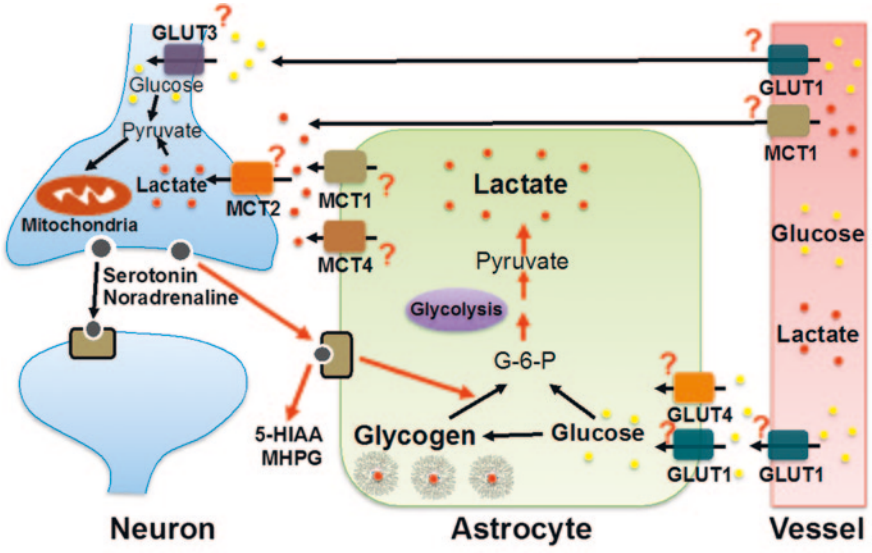

Fig. 1 Glycogen metabolism in the brain: contribution to astrocyte–neuron lactate shuttle. glucose-6-phosphate (*G-6-P*), Glucose transporter (*GLUT*), monocarboxylic acid transporter (MCT) energy sources for neurons include not only blood glucose but also lactate. Astrocytic glycogen is synthesized from blood glucose and degraded into lactate by excitatory neurotransmitters such as noradrenaline and serotonin. Lactate is uptaken neurons and changed to pyruvate, which is used for ATP synthesis in the mitochondria. The effect of exercise on GLUTs and MCTs in the brain is not elucidated yet

involved in determining the post-mortem brain glycogen levels in animal tests, because brain glycogen is metabolized rapidly following death. The current optimal method is to snap-inactivate glycogen-metabolizing enzymes using high-power (10 kW) microwave irradiation (MI) (Kong et al. 2002; Matsui et al. 2011). Here, MI enabled us to inhibit glycogen metabolism after animal death by elevating brain temperature to approximately 90 °C within 1 s, which allowed us to take accurate measurements of brain glycogen levels.

Physiological Role of Brain Glycogen

Animal studies using MI have shown that astrocytic glycogen is degraded into lactate to provide fuel for neurons during hypoglycemia, sleep deprivation, and memory formation (Brown 2004). Interestingly, neuronal activation in the cortex during hypoglycemia was prolonged when the basal level of brain glycogen was elevated (Suh et al. 2007). Furthermore, the inhibition of hippocampal glycogen degradation in rats with 1,4-dideoxy-1,4-imino-d-arabinitol (DAB, a glycogen degradation inhibitor), interdicted long-term memory formation (Suzuki et al. 2011). Collectively, these results evidence that astrocytic glycogen is a critical energy source for neurons when the glucose provision from blood is insufficient and when there are sudden increases in energy demands during neuronal activation.

Brain Glycogen Decrease During Prolonged Exhaustive Exercise

Exercise increases the brain's energy demands through neuronal activation, and prolonged exercise induces hypoglycemia, leading us to postulate that brain glycogen decreases during exercise. To test this hypothesis, we exercised male Wistar rats on a treadmill for different durations (30–120 min) at moderate intensity (20 m/min) and measured their brain glycogen levels using MI (Matsui et al. 2011). At the end of 30 and 60 min of running, blood glucose levels did not decrease compared with those of pre-exercise, but at the end of 120 min, blood glucose was 46 % lower than pre-exercise levels. After 30 and 60 min, brain glycogen levels remained unchanged from resting levels, but liver and muscle glycogen decreased. After 120 min, brain glycogen levels decreased significantly by an average of 34–60 % in five discrete brain loci (the cerebellum 60 %, cortex 48 %, hippocampus 43 %, brainstem 37 %, and hypothalamus 34 %) compared to those of pre-exercise levels (Fig. 2a). Figure 2b shows image data of brain glycogen staining, and we can see glycogen decreases especially in the cortex, hippocampus, cerebellum, and brainstem. The brain glycogen levels after running in all five regions were significantly correlated with the respective blood glucose (positive) and with brain lactate levels (negative) (data not shown). Further, in the cortex, the levels of metabolites of

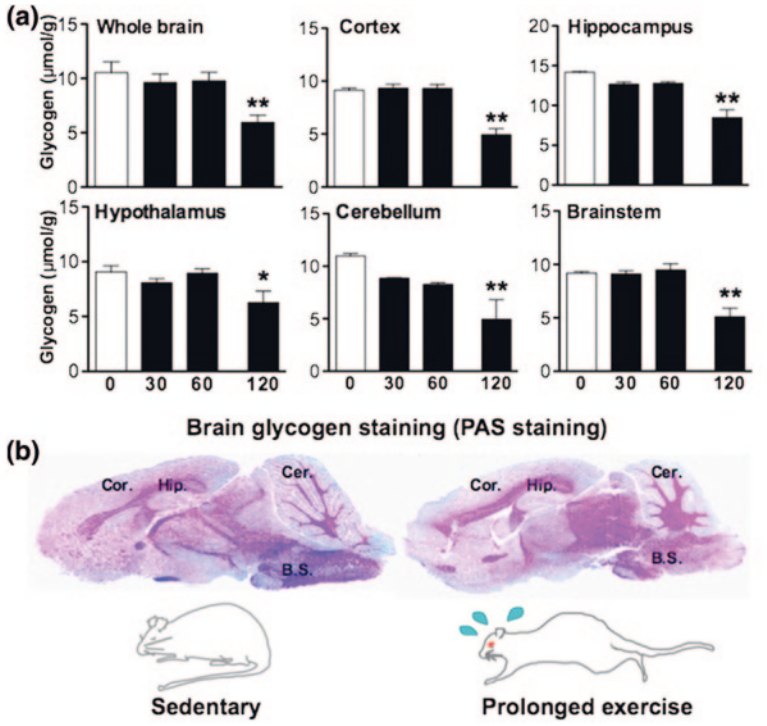

Fig. 2 Brain glycogen decreases during prolonged exercise. **a** Brain glycogen levels. Data represent the mean ± SEM (n = 5–6 rats). * $p < 0.05$; ** $p < 0.01$ compared to pre-exercised rats (Dunnett's post hoc test). **b** Brain glycogen staining (periodic acid-Schiff (*PAS*) staining)

noradrenaline (methoxyhydroxyphenylglycol; MHPG) and serotonin (5-hydroxyindoleacetic acid; 5-HIAA), which are potentially involved in the degradation of brain glycogen, increased during prolonged exercise and negatively correlated with glycogen levels (data not shown). This supports the hypothesis that brain glycogen decreases with prolonged exhaustive exercise, and suggests that increased noradrenaline and serotonin together with hypoglycemia is associated with glycolysis in the brain (Matsui et al. 2011) (Fig. 1).

Brain Glycogen Decrease and Central Fatigue

Brain glycogen decrease may be an integrative factor of central fatigue during prolonged exercise. Until now, hypoglycemia with muscular and liver glycogen depletion, an increase in brain serotonin (serotonin hypothesis), and a high brain temperature (hot brain) have been recognized as factors inducing central fatigue

during prolonged exercise (Newsholme et al. 1992; Nybo and Secher 2004). These are very interesting as a complex phenomenon influenced by both peripheral and central factors. On the other hand, hypoglycemia and serotonin are not only inducing factors of central fatigue but also enhancing factors of astrocytic glycogen degradation. Thus, brain glycogen decreases with prolonged exercise lead us to postulate that hypoglycemia together with brain activation with noradrenaline and/or serotonin metabolism may be involved in the development of decreased brain glycogen, and may shed light on studies examining how brain glycogen metabolism is involved in central fatigue during exercise (Fig. 3) (i.e., understanding how enhancing the effects of brain glycogen storage and availability may delay exercise-induced exhaustion).

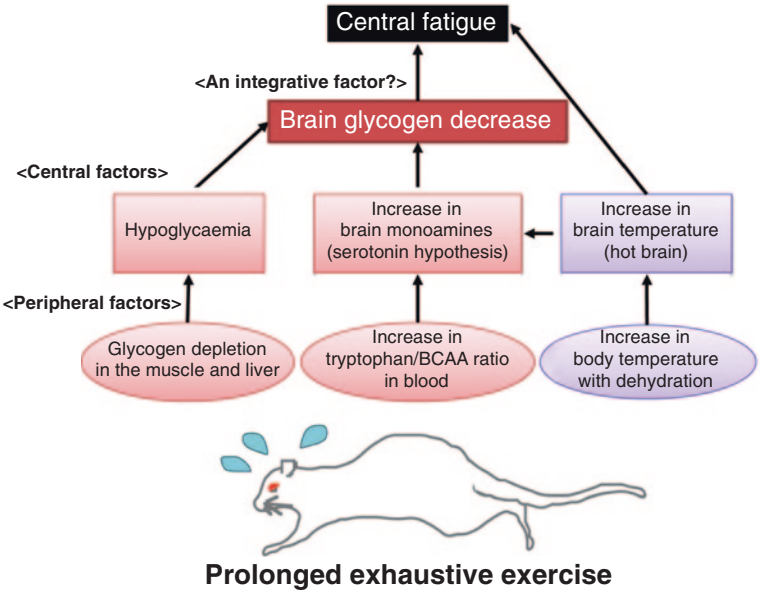

Fig. 3 Hypothetical diagram showing the brain glycogen decrease as an integrative factor of central fatigue during prolonged exercise. Prolonged exercise induces glycogen depletion in the muscles and liver, and hypoglycaemia, which causes peripheral fatigue. Hypoglycemia elicits energy shortages in the brain, and likely induces central fatigue. Increase in brain serotonin due to rise in tryptophan/branched-chain amino acid (*BCAA*) ratio in blood also induces central fatigue by eliciting lassitude (serotonin hypothesis). Furthermore, increases in body and brain temperature attributed dehydration induce central fatigue directly and/or indirectly through increases in brain noradrenaline and serotonin. Hypoglycemia and serotonin are not only inducing factors of central fatigue but also enhancing factors of astrocytic glycogen degradation. Indeed, we observed that brain glycogen levels after running were correlated with the respective blood glucose and increased serotonin metabolism (Matsui et al. 2011). Exercise-induced brain glycogen decrease could be an integrative factor of central fatigue

Brain Glycogen Supercompensation Following Prolonged Exhaustive Exercise

In the next step, we tested the above-mentioned hypothesis, and found that brain glycogen supercompensation occurs following exhaustive exercise like in skeletal muscles, and the extent of supercompensation is dependent on that of glycogen decrease during exercise (Matsui et al. 2012).

The extent of post-exercise brain glycogen supercompensation is dependent on that of glycogen decrease during exercise, across brain regions (Matsui et al. 2012). Greater glycogen depletion induces greater glycogen supercompensation in skeletal muscle (Goforth et al. 2003), suggesting muscle glycogen supercompensation is inducible in more active muscle for metabolic adaptation. In our data, the highest rate of glycogen decrease and supercompensation was seen in the cerebellum (64 vs. 63 %), the second highest was in the cortex (61 vs. 60 %) and the lowest was seen in the hypothalamus (50 vs. 29 %). Vissing et al. (1996) examined glucose utilization as an index of functional neuronal activity during 30 min of high-intensity running (28 m/min, $\sim$ 85 % of maximum oxygen consumption), and found that cerebellar and cortical glucose utilization are higher than hypothalamic use. Thus, in the brain, greater neuronal activity could induce greater glycogen supercompensation as seen in skeletal muscle.

During the recovery phase after exhaustive exercise, glycogen supercompensation in the brain occurs earlier than that of skeletal muscles and the liver (Brain:Skeletal muscle:Liver = 6 h:24 h:24 h onwards; Fig. 4). These results are consistent with the previous findings that skeletal muscles exhibit glycogen supercompensation at 24 h after exhaustive exercise (Gaesser and Brooks 1980), and that the brain exhibits rapid glycogen replenishment and supercompensation at 4–7 h after insulin-induced hypoglycemia in rats (Choi et al. 2003; Canada et al. 2011). These findings support the "Selfish Brain Theory" regarding competition for energy resources throughout the whole body (Peters et al. 2004). Brain glycogen depletion with severe, insulin-induced hypoglycemia elicits neuronal death (Suh et al. 2007). Severe hypoglycemia in animals and humans induces a hypoglycemic coma to save energy, and ultimately their life (Sokoloff 1971). Thus, rapid and preferential brain glycogen supercompensation following exhaustive exercise with hypoglycemia may also be induced in an attempt to prevent neuronal death and to save the animals' lives (preservation of species), and could cause metabolic adaptation in the brain for delaying hypoglycemic coma.

Exercise Training Increases Basal Level of Brain Glycogen

We also observed that cortical and hippocampal glycogen supercompensation were sustained until 24 h after exercise (long-lasting supercompensation), and their basal glycogen levels increased with 4 weeks of exercise training (60 min/d, 5 d/wk at 20 m/min) compared to sedentary rats (Matsui et al. 2012).

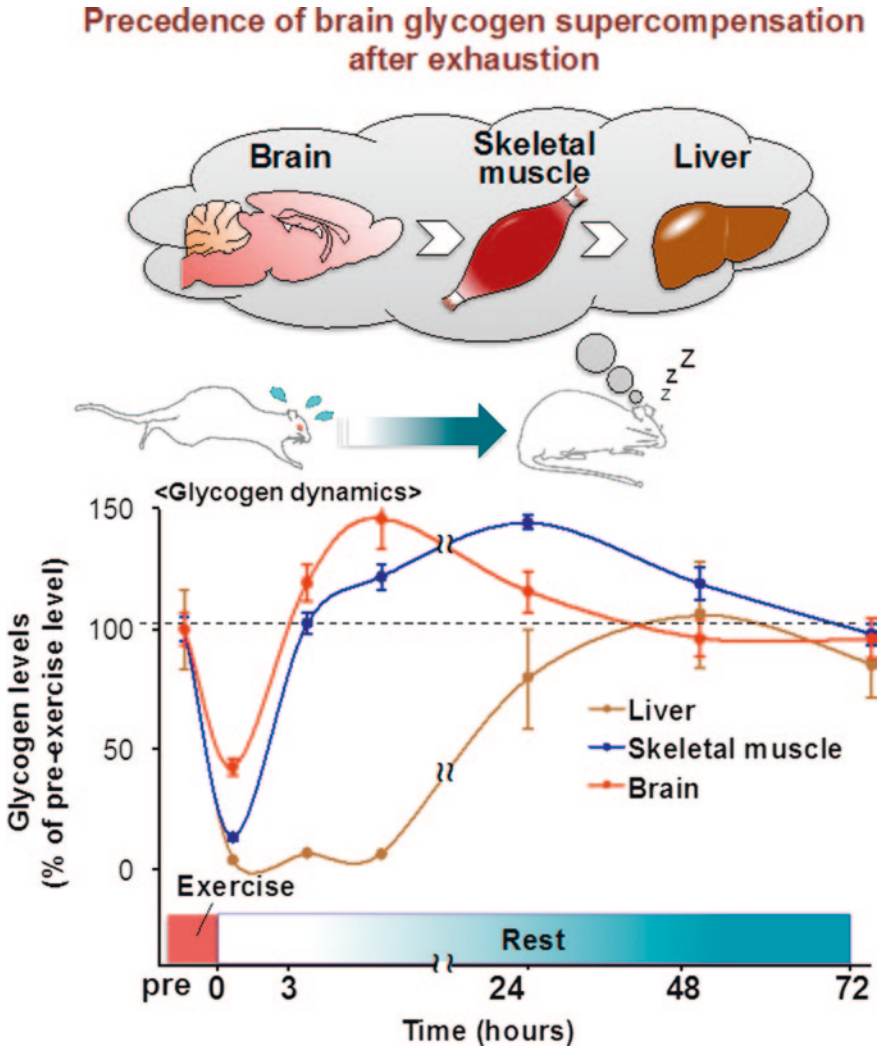

Fig. 4 The glycogen dynamics during and following exhaustive exercise in the brain, skeletal muscle, and liver. Data from pre-exercise to 24 h after exercise are taken from an our previous study (Matsui et al. 2012), and data from 48 to 72 h after exercise are extrapolated based on our unpublished data. During exhaustive exercise, brain glycogen decreases by approximately 50–60 %, while glycogen in skeletal muscle and liver decreases by approximately 80–90 %. Following exercise, in the resting phase, skeletal muscle glycogen supercompensation occurs at 24 h after exercise, and returns to pre-exercise level at 72 h after exercise. Brain glycogen supercompensation also occurs and reaches the peak of supercompensation at 6 h after exercise, and returns to pre-exercise level at 48 h after exercise. Liver glycogen is not completely replenished until 48 h after exercise

Perhaps, increased basal glycogen levels in the cortex and hippocampus with exercise training are a result of the accumulation of long-lasting supercompensation with acute exercise. In the exhaustive exercise test, the long-lasting glycogen supercompensation following exhaustive exercise was confirmed at 24 h after exercise in the cortex and hippocampus, but not in the cerebellum, hypothalamus, or brainstem (Matsui et al. 2012). In a previous study, without MI, glycogen supercompensation in the whole brain was confirmed following insulin-induced hypoglycemia, but long-lasting supercompensation was not observed (Canada et al. 2011). These findings suggest that the long-lasting glycogen supercompensation could be an exercise specific effect with exercise-induced neuronal activation in the brain.

Increased brain glycogen levels must be adaptive metabolic changes in the brain in response to increased energy demand with endurance training. Increases in cortical and hippocampal glycogen levels accompany the typical indications of endurance training, such as reduced body and fat weights, and increased wet weights, glycogen levels, and CS activity in the soleus muscle (slow-twitch type) (James and Kraegen 1984; Siu et al. 2003; Matsui et al. 2012). Brain mitochondrial biogenesis increases with exercise training, as in skeletal muscle (Davis et al. 2009; Steiner et al. 2011). In addition to increased mitochondrial biogenesis, an increase in brain glycogen with exercise training could be an important phenomenon of the adaptation to meet the increased energy demands of the brain in exercising animals. If so, the mRNA and protein content of glucose transporters and monocarboxylic acid transporters in astrocytes and neurons might also increase for activation of glycogen metabolism. However, these were not examined here, because the heat of MI would have broken mRNA and protein. We are examining whether the detection of mRNA and protein in the microwaved brain is possible.

Increased basal glycogen levels in the cortex and hippocampus with exercise training could have an important implication for their function. Cortical neuronal activation time during hypoglycemia was increased by elevating the basal level of cortical glycogen with the injection of a glycogen phosphorylase inhibitor (Suh et al. 2007). Thus, we can hypothesize that increased basal levels of cortical glycogen in exercise-trained animals prevents the attenuation of neuronal activity in the cortex during prolonged exercise with hypoglycemia and sustains central command from the motor cortex to skeletal muscles, and that this is a mitigating factor of central fatigue. An increase in the basal level of cortical glycogen may enhance endurance performance. On the other hand, an exercise-training-induced increase in hippocampal glycogen may be involved in cognitive function. It is well-known that exercise training enhances cognitive function, especially hippocampal function (van Praag, 2009). Hippocampal glycogen levels in Zucker rats, a type 2 diabetes model animal, were lower than those seen in control rats, which may be related to the decline of cognitive function in these animals (Sickmann et al. 2010). Furthermore, the inhibition of hippocampal glycogenolysis in rats by 1,4-dideoxy-1,4-imino-d-arabinitol (DAB, a glycogen phosphorylase inhibitor), interdicted long-term memory formation (Suzuki et al. 2011). Therefore, it

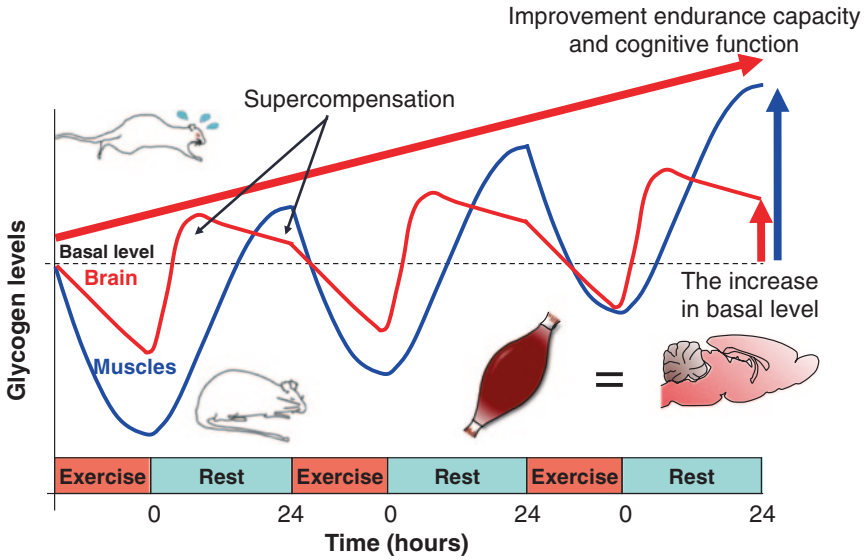

Fig. 5 The training adaptation of brain glycogen like in the skeletal muscle. Brain glycogen decreases during prolonged exhaustive exercise, and supercompensates with rest following that. Exercise training-elicited metabolic adaptation (increase in basal level of glycogen) in the brain like in skeletal muscles should be based on glycogen decrease and long-lasting supercompensation in the cortex and hippocampus

is tempting to speculate that increased hippocampal basal glycogen might be involved in promoting cognitive function with exercise training.

Collectively, we have provided evidence for the first time that brain glycogen supercompensation occurs in the brain, like in skeletal muscle, following exhaustive exercise. Furthermore, the lower the brain glycogen level during exercise, the higher the extent of glycogen supercompensation after exercise. In addition, the brain glycogen supercompensation peak preceded that of skeletal muscles and liver. We also propose that long-lasting glycogen supercompensation is likely a prerequisite for training adaptation (increased basal levels), probably to meet the increased energy demand of the brain in exercising animals (Fig. 5).

Hypothetical Molecular Mechanisms for Brain Glycogen Supercompensation Following Exhaustive Exercise

Underlying molecular mechanisms behind brain glycogen replenishment and supercompensation are controversial, with limited information provided by in vitro studies. Among them, insulin and insulin-like growth factor I (IGF-I) have been implicated in the regulation of astrocytic glycogen synthesis as well as that

of peripheral organs (Dringen and Hamprecht 1992). However, we could not find a correlation between blood insulin and supercompensated brain glycogen levels during glycogen repletion after exercise, although we found a positive correlation between blood insulin and liver glycogen levels ($r = 0.64$, $p < 0.01$) (data not shown). On the other hand, we found that regional blood–brain barrier transport of IGF-I was enhanced by neuronal activation during exercise and/or exposure to an enriched environment (Nishijima et al., 2010). Thus, we should explore whether IGF-I's signaling is involved in the replenishment and supercompensation of brain glycogen.

Further, it is of interest that the neurotransmitters NA and vasoactive intestinal peptide (VIP), which have been identified as neuronal signals triggering glycogenolysis in astrocytes, causes the induction of protein targeting to glycogen (PTG) in a non-insulin dependent fashion and the subsequent enhancement of glycogen synthesis in primary culture of astrocytes (Sorg and Magistretti 1992; Allaman et al. 2000). NA and its metabolism in the brain has been shown to increase during exercise (Pagliari and Peyrin 1995; Matsui et al. 2011). Thus, it is hypothesized that increased cerebral NA once stimulates astrocytic glycogenolysis during exhaustive exercise and expression of PTG, which may in turn lead to glycogen supercompensation.

In this chapter, we introduced animal experiment data regarding brain glycogen decrease and supercompensation with prolonged exhaustive exercise. A human study using nuclear magnetic resonance (NMR) also showed brain glycogen decrease and supercompensation with insulin-induced hypoglycemia (Oz et al. 2009). Thus, it is possible that exercise-induced brain glycogen decrease and supercompensation also occurs in humans. It may soon be possible to propose new concepts such as "brain glycogen loading" to mitigate central fatigue during exercise.

Highlights

- Astrocytic glycogen, which is a crucial energy storage in the brain, decreases to supply a lactate as a energy source for neurons during prolonged exercise with hypoglycemia.
- The brain glycogen decrease could be an integrated factor of the central fatigue during prolonged exercise.
- The decreased brain glycogen recovers to above basal levels (supercompensation) with a rest after exercise, and that timing is earlier than that of skeletal muscles.
- The glycogen supercompensation in the crotex and hippocampus is sustained until 24 h after exercise (long-lasting supercompensation).
- Exercise training increases basal levels of glycogen in the cortex and hippocampus, suggesting training adaptation probably to meet the increased energy demand of the exercising brain.

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Chapter 16
Resistance Training and Cognitive and Cortical Plasticity in Older Adults

Teresa Liu-Ambrose and Lindsay S. Nagamatsu

Introduction

Research on the diverse health benefits of physical activity has exploded in recent years. While it is widely recognized that exercise has multiple health-related benefits, there is now a strong interest in its effect on cognitive function (Colcombe et al. 2004; Erickson et al. 2011; Liu-Ambrose et al. 2010; Liu-Ambrose et al. 2012; Nagamatsu et al. 2012). Cognitive decline is a major health-care concern, especially given our aging baby-boomer population; the potential impact of cognitive decline on health-care systems and quality of life cannot be overstated. According to the World Health Organization and the Alzheimer's Disease International (World Health Organization 2012), one new case of dementia is detected every four seconds worldwide. Additionally, the number of people affected is projected to be over 80 million by 2040 (Ferri et al. 2005). Hence, identifying effective strategies to prevent or delay the onset of cognitive decline is an increasing priority.

Physical activity has been widely promoted as a strategy for healthy aging as it can reduce the incidence of cancer, diabetes, and heart disease (Booth et al. 2000). In recent years, there has been a strong interest in physical activity as a primary behavioral prevention strategy against cognitive decline. Targeted exercise training is a promising strategy for combating cognitive decline. There are two distinct forms of exercise training: (1) aerobic training (e.g., running), aimed at improving cardiovascular health, and (2) resistance training (e.g., lifting weights), aimed at improving muscle strength. However, the majority of research on exercise and cognitive function has focused on aerobic training, defined as cardiovascular exercise where the heart rate is raised (Colcombe and Kramer 2003). Examples of aerobic training include walking, running, or biking. Yet, not all older adults have the necessary mobility to participate in targeted aerobic training at the recommended intensities

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and duration. Thus, other types of targeted exercise training must be considered and evaluated. Auspiciously, there is a growing interest in the role of resistance training (Liu-Ambrose and Donaldson 2009) and recent research findings indicate that it is beneficial for both cognitive and functional brain plasticity (Liu-Ambrose et al. 2010; Liu-Ambrose et al. 2012; Nagamatsu et al. 2012).

Aside from its neurocognitive benefits, resistance training may be a particularly important mode of exercise for seniors as it specifically moderates sarcopenia (i.e., age-related loss in both muscle mass and strength), whereas aerobic training does not. The multifactorial deleterious sequelae of sarcopenia include increased falls and fracture risk as well as physical disability. For more than a decade in the US, resistance training has been recommended for adults, particularly seniors, as a primary prevention intervention, and increasing the prevalence of resistance training is an objective of Healthy People 2010 (United States Department of Health and Human Services 2010).

In this chapter, we will provide an overview of the current evidence (i.e., randomized controlled trials) for the effects of resistance training on cognitive function in seniors, discuss the possible underlying mechanisms, and conclude with limitations and future directions for this rapidly expanding line of research. As we delve into the specific randomized controlled trials, one should consider the following factors along with the study findings: (1) training duration; (2) training intensity; (3) training frequency; (4) sample size; and (5) target population.

The Effects of Resistance Training on Cognitive Function

To our knowledge, all of the research on resistance training and cognition has been restricted to seniors. Two main reasons for this bias include: (1) combating cognitive decline is an increasing priority in our rapidly aging population; and (2) there is a misconception that resistance training is unsafe for those who are still developing (i.e., children and young adults). Hence, we will summarize the current research on the effects of resistance training on cognitive function in seniors, with a focus on randomized controlled trials.

Evidence that Resistance Training Improves Cognitive Function

In one of the earliest randomized controlled trials of exercise and cognition that included a resistance training component, community-dwelling senior men and women significantly improved their working memory performance after 12 months of training (Williams and Lord 1997). Specifically, participants completed a community-based exercise program that included aerobic, strength, and stretching components. While participants did significantly improve their working memory, as measured by the Digit Span Backwards test, there were no changes in performance on the Picture Arrangement or Catell's Matrices tests—which measure nonverbal

reasoning ability and problem solving, respectively. This study was a great first pass for introducing the concept that resistance training may be a critical component of an effective exercise regime. However, the exercise program in this trial was multidimensional by design, which means we cannot disentangle the benefits of each type of exercise on cognitive function. In addition, the program was focused on social involvement, and their control group was a no-contact group. Therefore, the authors concluded that social interaction may have played a role in their results.

Nevertheless, it is noteworthy that a meta-analysis (Colcombe and Kramer 2003) of randomized controlled trials found that aerobic exercise programs that were combined with resistance training had a greater positive effect on cognitive function than aerobic exercise alone (effect size = 0.59 vs. 0.41, SE = 0.043, $P < 0.05$). Furthermore, work by Liu-Ambrose and colleague (Liu-Ambrose et al. 2008) demonstrated that an individualized home-based program of balance and resistance training exercises, known as the Otago Exercise Program (Campbell et al. 1997), significantly improved the executive cognitive processes of selective attention and conflict resolution as measured by the Stroop Colour Word Test after 6 months among seniors aged 70 years and older with a recent history of falls. The finding of this single-blinded randomized controlled trial is notable given that many have hypothesized that the cognitive and neural benefits of exercise must occur within the context of social engagement for the effects of the exercise to be effective (Fabel and Kempermann 2008).

Another key randomized controlled trial supporting the hypothesis that resistance training is beneficial for cognitive function was conducted by Cassilhas and colleagues (Cassilhas et al. 2007). They demonstrated that resistance training three times per week for 24 weeks significantly improved several measures of cognitive function among 62 community-dwelling senior men aged 65–75 years, including Corsi's Block-Tapping Task Backward, Similarities, Rey-Osterrieth Complex Figure Immediate Recall, Toulouse-Pieron Concentration Test Errors, and Digit Span Forward. Interestingly, comparable benefits were observed for both high- and moderate-intensity groups, defined as 80 and 50 % of single-repetition maximum lift (i.e., 1 RM), respectively. Results from this study suggest that even moderate-intensity resistance training for a relatively short time period, such as 6 months, can have a significant impact on cognitive function. Using a protocol similar to that of Cassilhas and colleagues (Cassilhas et al. 2007), recent work by Busse and colleagues (Busse et al. 2008) suggests that resistance training may also be beneficial for sedentary older adults at greater risk for Alzheimer's disease—those with objective mild memory impairment.

Extending the work of Cassilhas and colleagues, Liu-Ambrose and colleagues (Liu-Ambrose et al. 2010) found that both once- and twice-weekly resistance training significantly improved the executive cognitive processes of selective attention and conflict resolution in senior women. Specifically, community-dwelling senior women participated in a 12-month trial that required them to engage in progressive resistance training either once or twice per week. Compared with a balance and tone control group, those in the resistance training groups performed significantly better on the Stroop Colour Word Test at trial completion. Changes in functional activation in cortex were also examined in each of the three groups (Liu-Ambrose et al. 2012). Interestingly, only the twice-weekly resistance training group showed

increased neural activation in two key regions of cortex integral for response inhibition—the anterior portion of the left middle temporal gyrus and the left anterior insula extending into lateral orbital frontal cortex. Thus, while resistance training once per week may improve executive functions at a behavioral level, twice-weekly training may be required for functional plasticity at the neural level.

Recent evidence suggests that the beneficial effects of targeted exercise training on cognitive and functional brain plasticity are not restricted to healthy older adults. In particular, there is now much interest in assessing the effect of exercise in individuals at risk for dementia, such as those with mild cognitive impairment (MCI). MCI is a well-recognized risk factor for dementia. Longitudinal studies report that seniors with MCI develop Alzheimer's disease at a rate of 10–30 % annually (Petersen et al. 1999; Busse et al. 2003), compared to 1–2 % of seniors without MCI (Petersen et al. 1999). MCI is characterized by cognitive decline that is greater than expected for an individual's age and education level, but does not significantly interfere with everyday function (Petersen et al. 2001). Thus, MCI represents a critical window of opportunity for intervening and altering the trajectory of both cognitive decline and loss of functional independence in seniors.

In senior women with probable MCI, Nagamatsu and colleagues (Nagamatsu et al. 2012) found that 6 months of twice-weekly resistance training significantly improved the executive cognitive processes of selective attention and conflict resolution compared to the balance and tone control group. They also found improvements in associative memory—or the ability to remember items that were previously presented simultaneously. In conjunction, regional patterns of functional plasticity were found in the resistance training group. Specifically, three key regions in cortex showed greater functional activation during the associative memory task after 6 months of training—the right lingual gyrus, the right occipital-fusiform gyrus, and the right frontal pole. Remarkably, the improvements observed in executive performance were after only 6 months of training in those with MCI, compared with 12 months in otherwise healthy seniors (Liu-Ambrose et al. 2010). Therefore, it appears that the benefits of resistance training can be observed earlier in those with a larger opportunity for change.

To summarize the research presented thus far, randomized controlled trials have found that resistance training can significantly improve cognitive function and functional brain plasticity in both healthy seniors and those with MCI. That said, there is also evidence to the contrary—that resistance training may *not* have an impact on cognitive function. We will highlight three of these studies now and possible contributing factors for the negative results.

Evidence that Resistance Training Does Not Improve Cognitive Function

First, Tsutsumi and colleagues (Tsutsumi et al. 1997) demonstrated that while 12 weeks of either high- or low-intensity resistance training had significant improvements for physiological measures and psychological well-being, it did not impact

cognitive function. In this trial, 42 sedentary senior participants were divided into either a high- or low-intensity group, defined as 75–85 % of 1 RM with 8–12 repetitions or 55–65 % of 1 RM with 12–16 repetitions, respectively. Participants completed the resistance training program using weight machines three times per week. Cognitive function was assessed using two tasks—mental arithmetic and mirror drawing. Both the small sample size and short intervention period used in this study are possible explanations for not observing changes over time in either cognitive task.

Second, Lachman and colleagues (Lachman et al. 2006) conducted a 6-month randomized controlled trial of home-based resistance training among 210 sedentary community dwelling older adults and also found no significant between group differences in working memory as measured by the Digit Span Backward test. In addition to sufficient training duration (i.e., 6 months or greater), the training intensity, or training load, may be a key requirement for cognitive benefits. Lachman and colleagues (Lachman et al. 2006) delivered a 35 min videotaped program of 10 exercises using elastic bands. Participants were instructed to use bands of greater resistance when they could complete greater than 10 repetitions of an exercise without significant fatigue. Compared with the protocols used by recent positive randomized controlled trials in healthy older adults, such as 50–80 % of 1 RM (Liu-Ambrose et al. 2010; Nagamatsu et al. 2012; Cassilhas et al. 2007), the program delivered by Lachman and colleagues (Lachman et al. 2006) is at a lower intensity. Interestingly, while the authors did not find differences in working memory between the two groups, they did find that within the resistance training group, higher resistance levels were significantly related to changes in memory performance during the intervention. These results suggest that resistance training and memory may be related, but due to the low-intensity nature of their exercise program and/or lack of sensitivity with a single cognitive measure, they may not have observed significan between group differences in their trial.

Finally, Kimura and colleagues (Kimura et al. 2010) demonstrated that 12 weeks of twice-weekly resistance training did not significantly improve the executive cognitive process of task-switching compared with health education classes. Similar to Lachman and colleagues (Lachman et al. 2006), Kimura and colleagues (Kimura et al. 2010) had conducted a well-powered trial ($N = 119$). However, the short training period likely was a factor in the null findings. Kimura and colleagues themselves concluded that the training duration was likely insufficient to induce changes in insulin-like growth factor 1 (IGF-1), a potential mechanism underlying resistance training and cognitive function.

In summary, negative trials of resistance training and cognitive function generally have shorter intervention periods, training protocols of lower intensity, or smaller sample sizes as compared with the positive trials.

Potential Underlying Mechanisms

Due to the lack of animal studies of resistance training, it is difficult to ascertain the specific biological mechanisms by which resistance training promotes cognitive and functional plasticity. However, in humans, resistance training reduces serum

homocysteine (Vincent et al. 2003) and increases levels of insulin-like growth factor 1 (IGF-1) (Cassilhas et al. 2007; Borst et al. 2001). Homocysteine is a naturally occurring amino acid found in blood plasma. Increased homocysteine levels are associated with impaired cognitive performance (Schafer et al. 2005), Alzheimer's disease (Seshadri et al. 2002), and cerebral white matter lesions (Wager et al. 2004). Specifically, in a 2-year prospective study, elevated homocysteine impaired neuropsychological functioning in otherwise cognitively intact seniors (Garcia et al. 2004). In rat models, elevated levels of homocysteine are neurotoxic (Kruman et al. 2000). In contrast, IGF-1 promotes neuronal growth, survival, and differentiation and improves cognitive performance (Cotman and Berchtold 2002). Critically, Cassilhas and colleagues (Cassilhas et al. 2007) found serum IGF-1 levels were higher in the resistance training groups than in the control group. More recently, there is much speculation that resistance training may promote cognitive function through the reduction of cardiometabolic risk (e.g., maintaining insulin sensitivity). However, much more research in both humans and animals is required to define the mechanisms underlying the cognitive benefit of resistance training in seniors.

Conclusions

Overall, there is accumulating evidence that resistance training can positively impact cognitive function and functional brain plasticity. However, future animal and human studies are needed to ascertain what biological mechanisms are responsible for changes in cognitive function secondary to resistance training. Furthermore, future work must focus on refining parameters of training for precise prescription (e.g., frequency, intensity, and duration of resistance training). Finally, more studies in clinical populations at significant risk for dementia (e.g., stroke) are needed.

Limitations, Recommendations and Future Directions

Currently, a key limitation in the literature regarding resistance training and cognitive function is the lack of quality randomized controlled trials. While there is a growing interest in the role of resistance training in the promotion of brain health, much more research is needed to clearly define its effectiveness, prescription, and biological mechanisms. Future randomized controlled trial should be designed with sufficient training duration (i.e., >6 months), intensity, frequency, sample size, and include candidate mechanistic outcomes (e.g., IGF-1, cortisol, etc.). Furthermore, future trials need to ensure bias is minimized (i.e., single-blinding and schedule classes to reduce contamination). More trials should also include specific populations at risk for dementia (e.g., MCI, chronic stroke survivors, etc.). Finally, in order to compare future trials, it would be helpful to establish a set of standardized set of cognitive measures and standardized exercise protocols among researchers.

Clinical and Policy Implications

Findings to date reinforce American College of Sports Medicine (ACSM) guidelines that encourage resistance training at least twice weekly for healthy seniors (Kraemer et al. 2002). A meta-analysis found that combined programs of aerobic-based exercise training exercises and resistance training exercises had a greater positive effect on cognition than programs of aerobic-based exercise training only (Colcombe and Kramer 2003). Thus, clinicians, public health practitioners, and policy makers should consider encouraging older adults to undertake both aerobic-based exercise training and resistance training not only for 'physical health', but also because of the almost certain benefits for 'brain health'. Individuals interested in taking up resistance training should consult with their family physician and may wish to review the *ACSM Position Stand: Progression Models in Resistance Training in Healthy Adults* (Kraemer et al. 2002).

Highlights

- Resistance training is recommended for adults, particularly seniors, as a primary prevention intervention.
- There is a growing interest in role of resistance training in the promotion of brain health.
- Recent randomized controlled trials demonstrate that resistance training can significantly improve cognitive function and functional brain plasticity in both healthy seniors and those with MCI.
- Negative trials of resistance training and cognitive function generally have shorter intervention periods, training protocols of lower intensity, or smaller sample sizes as compared with the positive trials.
- For exercise to be medicine, future work must focus on refining the parameters of resistance training for precise prescription to combat cognitive decline.

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Part VI
Methods Primer

Chapter 17
Brain Imaging: A Primer

Lorin Elias

Not everything that can be counted counts,
And not everything that counts can be counted.

Albert Einstein.

The term "brain imaging" is a bit of a misnomer. The techniques described in the following chapter do create images of the brain, but the images are often not particularly representative of the brain's visual form. Instead, these images tend to be digital renderings of measurements taken of the (usually) living brain, documenting how many X-rays successfully passed through a given region, the relative proton density of various brain structures, how much electromagnetic activity can be measured at a particular spot and time, or even how much change in blood-flow follows the performance of a cognitive task. These resultant images represent the physical density, electrical activity, or hemodynamic responses of the brain, but none of them are particularly accurate visualizations of the *appearance* of the brain. In this way, 'imaging' is a somewhat inaccurate term to describe the brain measurement and subsequent renderings that follow these measurements.

This is a good thing. Representative images of the brain's physical form are not particularly useful when relating brain function to behavior. Functional neuroimaging provides the researcher with *in vivo* (live) pictures of the brain areas most or least active during a cognitive task. When this type of imaging was just starting to become popular, some predicted that it would rapidly put an end to experimental neuropsychology and cognitive neuroscience. It most certainly has not. The task of human brain mapping has been revolutionized by neuroimaging, but the job of mapping the human brain is far from over, and current imaging methods have a number of technical and methodological limitations.

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This chapter explores the various means by which neuroscientists can measure (or at least infer) activity in the human brain. Although it might be tempting to compare these methods to one another, looking for the 'best' method, these comparisons are not particularly informative. Instead, each method has its own unique combination of costs and benefits, and the 'best' method depends on the question being asked. For example, when attempting to diagnose epilepsy, a very expensive and flexible technique such as functional Magnetic Resonance Imaging (fMRI) is not very effective, but a much cheaper and simpler technique like an electroencephalograph (EEG) does an excellent job.

Structural Imaging

Structural neuroimaging involves taking a measurement of the brain to produce an image of its structure, regardless of the functions of those structures. Some examples of structural imaging include X-rays, computerized tomography:

X-rays. The field of **Neuroradiology** (studying the nervous system with imaging) was born following a serendipitous discovery made by a physicist, Wilhelm Conrad Röntgen (1845–1923) in 1895. While studying cathode rays, he noticed a glowing fluorescent screen on a nearby table. He quickly deduced that the fluorescence was coming from his partially evacuated glass Hittorf-Crookes tube, and that the rays from the tube could penetrate the thick black paper that was wrapped around the tube. This discovery earned Röntgen the first Nobel Prize in physics in 1901.

Although the discovery of X-rays had a tremendous impact on medicine, conventional X-rays did not prove to be very useful for neuroimaging. X-rays are very useful when looking for bone fractures, but a 2-D X-ray of the skull provides relatively little information about what is encased within the skull. In the early 1970s, Godfrey Housnfield and Allan Cormack independently pioneered the approach of taking multiple X-ray images from different angles, combining them to form a 3D image, which earned them Nobel Prize for physiology or medicine in 1979 (Finger 2000).

Computed Tomography (CT). Computed Tomography (CT) scans were the first good means available to non-invasively image live brain tissue. CT scanning and X-rays employ the same types of radiation and measures, but CT scanning involves the projection of X-rays from multiple angles followed by the computerized reconstruction of the measures into three-dimensional (3-D) images. The brain images are typically constructed in a number of "slices", in three different "planes'' of imaging (see Fig. 17.1). Images taken in the horizontal plane (running parallel with the horizon) are called **"axial"**. Most early CT images were constructed in this plane, but now they are often constructed in two other planes as well. Images in the **coronal** plane show slices perpendicular to the horizon, taken along the superior–inferior axis. Images in the **sagittal** plane are also perpendicular to the horizon, but they are taken along the dorsal–ventral axis.

CT scans offer a measurement of the densities of various tissues. Highly dense areas (such as the skull) appear bright, whereas areas of lower density (such as

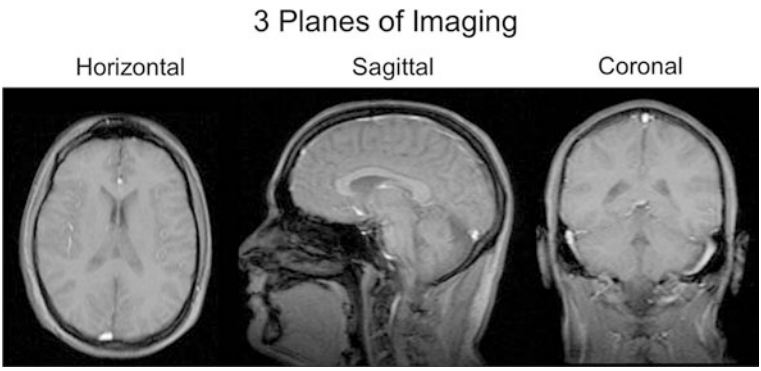

Fig. 17.1 3 planes of imaging

CSF and brain matter) appear relatively dark. The spatial resolution provided by CT scanners is often adequate for clinical purposes (between 0.5 and 1.0 cm), but its differentiation between white matter and gray matter is rather poor.

Magnetic Resonance Imaging (MRI). Magnetic Resonance Imaging (MRI) is a technique based on the Nobel Prize winning (Physics in 1952) research of Felix Bloch and Edward Purcell who developed methods for nuclear magnetic precision measurement. Some 20 years later, their discoveries were applied to medical imaging. It was initially called "nuclear Magnetic Resonance Imaging" (nMRI), but the term "nuclear" was dropped from the name because individuals find the word 'nuclear' unsettling (Maier 1995). Although people often confuse MRI scans with CT scans (presumably because they can produce a similar looking product), the two methods image the brain in fundamentally different ways. Further, MRI scanners are now widely regarded as a replacement for antiquated CT scanners because of their superior resolution, although CT scanners are still preferable in some situations.

As the name implies, MRI exploits the fact that many elements (such as hydrogen) can be influenced by magnetic fields. Hydrogen is an incredibly common element in the body, present in water, blood, tissue, bone—almost every compound in the human body. Normally, hydrogen atoms are *not* polarized. However, when placed in a strong magnetic field, the atoms become aligned. Once they are aligned, the atoms can be perturbed in a uniform direction through the application of a radio frequency pulse. Different pulse frequencies are better at perturbing hydrogen atoms within different types of substances, depending on what you want to image (such as water or deoxygenated blood). What the MRI machine actually measures is the **relaxation time** that follows the pulse, which is the time taken by the atoms to return to their normal, random state. The MRI's **receiver coil** measures the information about the intensity of the signal, but the spatial information is provided from variations in the **gradient field** over the imaged area. The combination of these two types of information allows the construction of 3D images of the brain (Perani and Cappa 1999).

Unlike CT scans, these images are not measures of brain density (electron density, to be exact). Instead, they are usually representations of hydrogen density. However, there are two other properties of the tissues that can influence the MRI signal. The relaxation time can reflect the return to a random state along the longitudinal axis (called T1 relaxation time, or spin–lattice relaxation) or along the horizontal plane (called T2 relaxation time, or spin–spin relaxation). Different substances 'relax' at different rates along these dimensions. Therefore, images of T1 relaxation look different and provide different information than images of T2 relaxation. On T1 images of the brain, bone, air, and water appear to be dark. On T2 images, air and bone still appear dark, but fluid appears to be quite bright. The type of relaxation that one chooses to image depends on what one is looking for. Some conditions (such as Alzheimer's disease) are more easily detected on T1 images, whereas other conditions (such as Parkinson's disease and arteriosclerosis) are more clearly visible on T2 images (Ketonen 1998; Perani and Cappa 1999; Vymazal et al. 1999).

MRIs contain extremely strong magnets, and their magnetic strength can be measured in units of **Tesla** (T). The earth's magnetic field is roughly .00005 T, whereas an everyday refrigerator magnet is some 100 times stronger—005 T. Most MRIs used for clinical purposes are another 300 times stronger, ranging from 0.5 to 1.5 T, whereas MRIs used for research purposes on humans can create strengths of 3.0–9.4 T (Novak et al. 2005).

Unlike CT scanning which exposes an individual to X-ray radiation, MRI scans are generally considered to be almost completely noninvasive. However, this does not mean that they are 100 % safe. Placing people in such strong magnetic fields can be very dangerous if they have pieces of metal in their body that can be attracted to a magnet. For example, if an individual with a metallic, magnetic aneurysm clip on a blood vessel in their head underwent an MRI, this could dislodge the clip. Heart pacemakers are also usually incompatible with MRI scanners. Surgical pins used to help set bones can also be problematic, but most metallic dental work (such as a filling) is magnetically inert. The MRI's very strong magnetic fields can also be dangerous if magnetic objects are brought into the scanning area. For example, with a 3.0 Tesla MRI, a 10-lb. hammer would get sucked into the magnet, striking the machine as hard as if it had the force of a half-ton object.

Diffusion Tensor Imaging

Conventional MRI scans produced detailed images of the structure of the brain, but these images provide little (if any) information about the ways that the various brain areas were connected to one another. A subtype of MRI called **Diffusion Tensor Imaging** (DTI) changed that, allowing investigators to trace the myelinated (white matter) connections between brain areas (Taylor and Bushell 1985). DTI measures the density and even the motion of the water that is contained

within the axons of the brain's neurons. Because the diffusion characteristics (the 'D' in DTI) of the water in the brain varies in a manner which is restricted by the membranes of the axons, this perpendicular laminar motion of the water can be imaged to represent the orientation of axon bundles within the brain. Imaging the brain in this way allows investigators to create a 'connection map' (at least the major myelinated connections) of the brain instead of merely an image of the density of the brain. Further, because DTI and conventional MRI can be obtained with the same equipment, during the same session, investigators can take advantage of converging methods.

This technique has proven to be very successful clinically, especially detecting disorders that selectively target white matter, but it has also been used to inform the clinical management of patients post-stroke. It has also become a very popular research tool, and a new field of functional DTI imaging (diffusion functional MRI, DfMRI) is currently emerging.

Electrophysiological Methods

Electrophysiological methods of investigating brain-behavior relationships involve measuring the electrical and/or magnetic currents generated by brain activity. These methods are typically described separately from functional imaging methods such as PET and fMRI that measure the brain's hemodynamic response (described in the next section), yet many argue (and rightfully so) that electrophysiology is also functional imaging. Traditional electrophysiological methods were less focused on localizing the source of the activity than they were at describing the *nature* of the activity (usually in terms of frequency, amplitude, and regularity). As you will see in the following sections, this focus is changing, subsequently blurring the line between electrophysiology and other functional imaging methods. However, the functional imaging methods described later in this chapter are qualitatively different from the electrophysiological methods described in this section. When making electrophysiological measurements, the changes caused by differences in blood flow are often considered a nuisance whereas quantifying such change is the *goal* of a variety of other functional imaging methods (e.g., PET, fMRI). Further, the weaknesses of most electrophysiological methods (i.e.,spatial resolution) are the strengths of most other functional imaging methods, whereas their strengths (i.e., temporal resolution) are weaknesses of the other methods.

Electroencephalogram (EEG). The first electrophysiological measures of brain activity were recorded as early as 1875 (Finger 1994). Richard Caton, a British physician and physiology lecturer recorded changes in electrical potentials from exposed brains of a number of animals. His work had little impact at the time, and it was later repeated and republished by Adolph Beck of Poland some 15 years later. Austrian psychiatrist Hans Berger became aware of Caton's work and attempted some similar experiments with non-human animals. After limited success, Berger decided to attempt to record the activity of human brains through

the intact skull. In 1929, he published the results he had obtained 5 years earlier using his son, Klaus, as his participant. Berger also tested a number of other people (including himself), and he discovered regular waves (roughly 10 cycles per second = 10 Hz) that he termed **alpha waves** because they were the first waves he isolated. Berger was quite concerned that blood circulation might be creating harmonics in the recordings, but he also recorded blood pressure from the head to control for that possibility. Despite these careful measures, Berger's work was very positively regarded at the time. He did not receive a Nobel Prize (unlike the scientists who helped to develop X-ray, CT, and MRI technology), but he was considered for the award twice. After a series of personal and professional setbacks, he committed suicide in 1941.

Berger developed a technique that is now called electroencephalography. In practice, electroencephalography results in an **electroencephalogram** (EEG). To record an EEG, small metal disks are attached to the scalp (usually using a paste), and the small changes in electrical potentials are amplified and recorded (either on paper or in digital form). The locations of the electrodes are standardized and generally organized in a symmetrical pattern, allowing the comparison of two analogous electrodes on opposite sides of the brain. One common standardized system for placing electrodes is called the 10–20 International Placement System. The "10" and "20" do not refer to the number of electrodes specified. Instead, they refer to the relative distances between the electrodes (10 or 20 % of distances between landmarks on the skull), and these distances must be calculated based on the head size of the person being tested.

Berger's original system for describing the 'brain waves' recorded during an EEG is still the best-known system. **Alpha** waves occur regularly at 8–13 Hz, **beta** waves refer to activity faster than 13 Hz (some now describe beta_1 as 13–16 Hz, beta_2 as 16–20 Hz, and beta_3 as >20 Hz). **Theta** waves are relatively slow at 4–8 Hz, and **delta** waves are the slowest at <4 Hz. In addition to describing these wave types, an EEG record might also include descriptions of **synchronization** or **desynchronization** between analogous sites (some degree of desynchronization is considered normal). Some EEG patterns are good indicators of convulsive disorders, such as epilepsy. One such pattern is **spike and wave activity**, wherein a short spike of high amplitude is immediately followed by a slow but high amplitude wave (Rippon 1999).

Event Related Potentials (ERPs). Recording **Event Related Potentials** (ERPs; also called **evoked potentials**) is a very similar procedure to recording EEGs. The two methodologies employ mostly the same equipment, and the measurement from the scalp is the same—small changes in electrical activity. The single biggest difference between recording EEGs and ERPs is that in an EEG, the person being recorded typically is *not* presented with any stimulation or cognitive task. The recordings are taken while the person is at rest, essentially measuring the 'idling brain'. However, if a person were to hear a loud noise during an EEG recording session, the perception of that noise would be reflected in the recording. However, because there is so much variability present in EEG recordings, these

changes are often very difficult (or impossible) to observe—there is too much 'background noise' in the recording.

ERP is an attempt to solve that problem. In order to study the brain's response to stimulation, a stimulus is presented *repeatedly* (sometimes hundreds of times) while simultaneously recording an EEG. The resultant EEG does not look much different from one without a stimulus, but if one looks at the *average difference* that follows the stimulation, a characteristic, slow waveform usually emerges. These waveforms are the "event related" or "evoked" response, and they typically last for less than 1 s after the presentation of the stimulus. The various components of the waveform (changes indicative of increases or decreases in voltage) are then named according to their **polarity** (positive or negative) and **time of onset**. An 'N100' component refers to a negative change occurring 100 ms after the stimulus presentation, whereas a 'P300' component would be a positive change after 300 ms (sometimes the two 0's are dropped, so the components are called 'N1' or 'P3').

These waveform components are often categorized into two types. **Exogenous components** are those associated with the physical characteristics of the stimulus. Therefore, altering the stimulus presented should alter the exogenous components of the waveform. **Endogenous components** are less dependent on the physical nature of the stimulus—instead, they appear to be determined largely by the cognitive task or context in which the stimuli are presented. As you might expect, these components are typically later in the waveform—after the initial sensation and perception of the stimulus. The distinction between endogenous and exogenous components of the waveforms is not always clear. Further, the source of the waveforms is often quite difficult to localize. The technique is good for studying relatively fast cognitive processes, such as attention and memory. It is also used to help diagnosis conditions such as multiple sclerosis, Alzheimer's disease, and Korsakoff's disease.

Magnetoencephalography (MEG). Unlike EEG and ERP, **MEG** does not measure the *electric fields* at the scalp. Instead, MEG measures the *magnetic fields* that are generated by the brain (Cohen 1972). Every current has an associated magnetic field that travels perpendicular to the current. These magnetic fields are very small, hard to measure, and normally difficult to distinguish from the small magnetic fields generated by nearby electronic devices (such as light bulbs, computers) or even the fields in the earth. For example, the magnetic field generated by the earth is more than a billion times stronger than those recorded from the brain's surface. To overcome this interference, MEGs are housed in rooms with thousands and thousands of pounds of shielding. The magnetic fields are detected using a **biomagnetometer**, which contains many small coils. The brain's magnetic fields induce tiny currents in these coils, and these currents create magnetic fields in arrays of **Superconducting Quantum Interference Devices** (SQUIDs). The SQUIDs only work at super-cooled temperatures. They are kept at −269 °C using liquid helium. As you might imagine, building and maintaining such a device is extremely expensive, even by medical-imaging standards!

MEG's primary advantage over other functional imaging methods is its temporal resolution—it is able to detect changes over periods as short as 1 ms. The technique's speed is not due to the expensive computers that run it—it is the nature of the response being measured. As you will see in the next section, measures related to changes in cerebral blood flow have much less temporal resolution because the changes in blood flow are relatively slow. MEG measures the magnetic fields associated with the firing neurons in the brain, and because electricity (and the associated magnetic fields) can change so quickly, this allows for unprecedented temporal resolution.

The spatial resolution provided by MEG imaging can also be impressive, but unlike other methods (such as CT, MRI, PET), its resolution degrades significantly as you infer function from deeper and deeper centers in the brain. One the surface of the brain (between 1 and 3 cm), MEG can resolve to a few millimeters (summing activity across approximately 50,000 neurons). However, deeper structures (for example, subcortical structures) cannot be measured with nearly that accuracy—the resolution is roughly 10 times worse. MEG's excellent temporal resolution and good spatial resolution for cortical structures toward the outer surface of the brain make it an excellent tool for studying primary sensory and motor cortical activity.

Functional Imaging

The functional imaging methods described in the next section infer brain activity without using measures of electrical currents or magnetic fields. For the most part, these methods are used measure changes in local blood flow. The brain does not store any oxygen, and it stores very little glucose. Therefore, neural activity must be supported immediately by the local blood supply. As energy demands increase, so too does blood flow. It would be ideal for researchers if there was a perfect relationship between energy metabolism and blood flow, but that is not the case. Supply tends to exceed demand. As energy requirements in a region of the brain rise, increases in local blood flow tend to exceed those requirements. Fortunately, this 'oversupply' phenomenon makes measures of blood flow very sensitive to changes in metabolism, perhaps even more sensitive than more direct measures (Frith and Friston 1996).

Positron Emission Tomography (PET). PET is a very flexible means for visualizing brain function. PET scans can provide a measure of local blood flow. However, PET scans are also capable of measuring the brain's utilization of other substances, such as glucose or dopamine. PET imaging involves a series of steps. First, one must label a compound with a positron- emitting radionuclide. The substances most often labeled for psychology experiments are oxygen, water, or glucose. Second, the substance must be administered (injected or inhaled) to the person to be scanned. Third, record the positrons emitted from the person's brain while they are in the scanner and use tomography to construct a 3D image of the activity (Phelps 2006).

The tracers used in PET have relatively short half-lives—the main radionuclides used in PET are Carbon 11 (^{11}C), Nitrogen 13 (^{13}N), and Oxygen 15 (^{15}O). Their half-lives are 20, 10, and 2 min, respectively, which allows for greater temporal resolution when imaging *changes* in blood flow. However, this comes at a cost. Because the tracers do not last very long, they need to be manufactured on-site using a machine called a **cyclotron.**

For an example, consider the most widely used tracer for PET imaging, $^{15}O_2$ (oxygen with one electron removed). $^{15}O_2$ is not a stable substance—sooner or later, it will release a positron to stabilize itself. Positrons are very rare and they don't tend to last very long—as soon as they come in contact with a free electron (which are common), they are annihilated. This process is fast—the average lifetime of a positron is a few hundred picoseconds (0.0000000003 s). There are two byproducts of the annihilation—two photons (also called *gamma rays*) that leave the scene of the collision perpendicular to one another. The photons are then detected using a system of detectors, and computerized tomography (just as in a CT-scan) is used to construct a 3D representation of the functioning brain.

PET imaging has a number of advantages over other functional imaging methods, but it also has major drawbacks. It can be used to study the brain's use of a wide variety of substances, but it is somewhat invasive, exposing people to ionizing radiation. Because of this exposure, people should not get many (more than 5) PET scans within a given year. Another drawback is that PET images of single participants tend not to be particularly revealing, usually due to poor signal-to-noise ratios. Therefore, using PET for research purposes usually require averaging responses across individuals. This characteristic of PET scanning also makes it less useful for clinical purposes.

Functional Magnetic Resonance Imaging (fMRI). The method for obtaining 'structural' MRI images (imaging proton density) was described in section Electrophysiological Methods, but MRI scanning is no longer limited to structural imaging. As MRIs became capable of faster image acquisition (using a technique called **Echo-Planar Imaging**, or EPI), what was previously a relatively *structural* imaging method could be now used for *functional* imaging (Perani and Cappa 1999; Stehling et al. 1991). The EPI technique involves ultra fast alternating magnetic gradients, using only one spin excitation per image acquired. **fMRI** uses much of the same equipment and methodology as does structural MRI. It also exploits the fact that many elements can be influenced by magnetic fields. After placing the participant's head in a strong magnetic field, polarizing the atoms, the atoms of interest are perturbed in a uniform direction through the application of a radio frequency pulse. The very first fMRI study measured changes in blood flow (the hemodynamic response) after giving participants intravenous injections of a paramagnetic contrast agent. The agent's concentration was detectable using T2 sensitive EPI sequences, and this allowed the investigators to track local changes in blood flow using MRI imaging. When the participants were exposed to visual stimulation, a localized increase in blood flow to the primary visual cortex was observed (Belliveau et al. 1991).

However, fMRI imaging is now normally completed *without* injecting any foreign agents. Oxygenated blood (containing oxyhemoglobin) and deoxygenated

blood (containing deoxyhemoglobin) have different magnetic properties. Using fMRI, the relative ratios of oxyhemoglobin and deoxyhemoglobin can be compared. Because local increases in metabolic activity are accompanied by local increases in blood flow, and these increases generally *exceed* the demand of the tissues being supplied. Therefore, areas exhibiting *increases* in oxyhemoglobin are probably also exhibiting increases in metabolic activity. There *is* a very brief period wherein active areas produce local levels of oxygen depletion, but this period is so short and small in magnitude, that the dominant hemodynamic response (and the one mostly measured in fMRI) is the local *increase* in oxygenation. The change in the relative concentration oxyhemoglobin to deoxyhemoglobin is often called the **Blood Oxygen Level Dependent** (BOLD) response (Huettel et al. 2009).

fMRI has several advantages over PET imaging. It can be performed using relatively common MRI equipment (available in the hospitals of most major urban centers in North America), does not require exposure to radiation or the injection/inhalation of tracers, it typically costs less than PET imaging, and the functional images can be superimposed over highly detailed anatomical images (allowing precise localization of the activity). Its temporal resolution is also far superior to PET, allowing much more precise mapping of the time course of patterns of activation across a network of interconnected nuclei.

However, fMRI also inherits the disadvantages of MRI. Individuals are subjected to very strong magnetic fields, making it impossible to scan individuals with pacemakers or other pieces of metal that are *not* magnetically inert. In fact, the magnetic field exposure in fMRI is even greater than that of MRI.

Challenges for Brain Imaging Studies

Most brain imaging studies share some of the same challenges. One common problem is that everyone's brain is different. Because there is no 'average brain', this creates a serious challenge for researchers who wish to use neuroimaging. What then does one do with functional neuroimaging from a group of 10 people? One person's brain might be substantially larger than that of another person in the same study. How you refer to common coordinates in 3-D space across brains of different size or shape? One common solution is to use the Talairach coordinate system (Talairach and Tournoux 1993) which uses anatomical landmarks like the anterior and posterior commissure to normalize brain scans to the atlas which was based on the brain of a 60 year-old French female (who had a slightly smaller than average brain). There are also other techniques for 'normalizing' brain scans to a common 3D space and atlas, but all the methods share the same disadvantages. All the methods introduce some warping or distortion of the original sample, and all the methods result in approximations of the borders between functional regions based on relative proximity instead of histological examination.

Functional imaging also faces additional challenges. One of them concerns how functional imaging data is summarized and presented. Consider the example

of how to communicate a dataset wherein *most* of the people (perhaps, 8 out of the 10) demonstrate similar patterns of activation (such as posterior parietal cortex activation), but the boundaries of functional brain areas are not in exactly the same location for each of the 10 people. What should the researcher do? Researchers have not come to a consensus on how to report the data. For instance, some researchers choose to describe each person separately, whereas others advocate create an average and composite image from the 10 people. Yet, other researchers try to categorize the people into groups and then create average composite images of the two groups.

Highlights

- Neuroimaging techniques have in common that they assist in characterizing the structure and function of the human brain.
- The most common methods are fMRI, EEG and PET. These each take fundamentally different approaches to imaging, and the superiority of each depends on the particular application.
- Becoming familiar with neuroimaging techniques may be useful for public health scientists who are interested in neuroscience research.

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Chapter 18
Survival Analysis in Social Neuroscience and Public Health: A Research Exemplar from the Field of Cognitive Epidemiology

Joel A. Dubin and Peter A. Hall

Much of the research in neuroscience is experimental in nature, while the bulk of research in public health is either purely observational or quasi-experimental. Survival analysis is one approach to a "time-to-event" analysis, commonly used in non-experimental medical and epidemiological research. Often we are concerned with understanding the relationship between a predictor variable and some time-based outcome variable of a dichotomous nature. The occurrence of the event in question can be potentially predicted by knowing a value on a relevant predictor variable(s). This is a situation wherein survival analysis can be applied. Despite its name, survival analysis is not only about tracking predictors of mortality. It can include any event whose occurrence is a discrete event, such as an acute health event or onset of chronic disease. Here we describe a classic application of survival analysis to the task of predicting mortality, but in this case our predictor of interest is a set of cognitive variables.

A Research Exemplar

One of the new and emerging areas of inquiry of interest to both public health and neuroscience is the field of *cognitive epidemiology* (Deary 2010). This field has been founded based on the premise that individual differences in cognitive function may predict a variety of outcomes of interest to epidemiologists, including mortality, susceptibility to illness, and survival in the context of illness. Over the course of the past 20 years, there has been an explosion of research in this area, and many findings that have challenged the way that we think about health and illness. One of the primary findings of this area has been that general cognitive

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ability (known at IQ, or *g* in the research literature) predicts many of the above-mentioned outcomes; specifically, those with stronger cognitive ability tend to live longer, engage in healthier behaviors, and are less susceptible to chronic illness and accidental death than those with weaker cognitive function (Batty et al. 2005, 2007a, b, 2008; Chandola et al. 2006; Gale et al. 2007; Hart et al. 2004; Hemmingsson et al. 2006; Lindgarde et al. 1987; Sorensen et al. 1983; Shipley et al. 2006; Starr et al. 2004; Taylor et al. 2003). Such effects, though relatively modest in magnitude, are largely independent of socioeconomic status, and a variety of other confounders.

Given that the focus of much of this research has been on the prognostic value of general cognitive function (*g*), or overall IQ, some have raised the question of whether or not it is possible that a more specific cognitive ability may be more predictive of health outcomes than global IQ. One specific ability that has been the focus of much interest within the field of health psychology has been executive function. Executive function is a set of top–down cognitive processes that facilitate control of thoughts, emotions, and behavior. Stronger executive function, or executive control resources (ECRs), have been shown to predict less frequent consumption of fatty foods (Hall 2012), better adherence to medication regimens (Hinkin et al. 2002; Insel et al. 2006), and more faithful adherence to behavioral prescriptions for exercise (McAuley et al. 2011) and other health-related behaviors (Hall et al. 2006). Moreover, it is known that subtests used to measure global IQ vary in the relative loading of ECRs (i.e., strong performance on each subtest requires strong ECRs, but more so on some subscales than others). The digit symbol (DS) subtest of the Wechsler Adult Intelligence Scale (WAIS; a recognised "gold standard" measure of global IQ), for example, is so strongly loaded with ECRs that it is sometimes used as a measure of ECRs itself. The question of interest is the following: does performance on this specific subtest account for the association between global IQ and all-cause mortality? In the particular application of survival analysis that we present here, we attempt to arrive at an answer for this question.

The analysis that we present is here from Hall et al. (2009). In this study we examined the prospective relationship among global IQ, each of its more specific subtests (DS, Block Design, Comprehension, and Similarities) and all-cause mortality among initially healthy and disease-free older adults. The follow-up interval for the study was 10 years, and the sample size was $N = 756$. Participants underwent an intensive baseline evaluation which included a detailed neurological investigation, neuropsychological assessment, and physical examination. Any individuals who had signs of dementia at baseline (actual or probable dementia) were excluded from this analysis, as were any individuals with a chronic illness indicated at baseline (leaving a usable subsample of $n = 516$ participants whom met the inclusion/exclusion criteria for the analysis). In the baseline examination, each IQ subtest was completed, and participants were followed for 10 years, tracking mortality using official records. We conducted survival analysis to determine the association between global IQ (taken as the sum of all four subtests) and each IQ subtest and mortality.

Logistic Regression and What is Often an Improved Model

To look at the association between a risk factor and disease, there are many available methods. In the fields of public health and medicine, arguably the most popular is logistic regression (e.g., Hosmer and Lemeshow 2000), which allows for examining at the association of interest while adjusting for potential confounders, sometimes several such confounders, as well as to consider important interactions among the risk factor and other predictors, if of interest. In such an analysis, the response is a binary outcome, such as disease-yes versus disease-no, and one attempts to ascertain whether certain combinations of covariates (e.g., poor nutrition, low levels of physical activity, etc.) are associated with a higher estimated probability of disease (e.g., Type 2 diabetes), while controlling for potential confounding variables (e.g., family history of diabetes, age, etc.).

A major limitation of logistic regression is that it defines responses on a narrow definition of the time domain. For example, if a cohort study is seeking to see if Type 2 diabetes-free individuals aged 25–40 years in a population are at risk for being diagnosed with Type 2 diabetes in the next 10 years, the definition of "disease" for purposes of a logistic regression analysis is fairly limited. That is, response will be disease-yes versus disease-no, where disease = being diagnosed with Type 2 diabetes at some point over the 10-year study follow-up period; a major limitation here is that it does not say when over the next 10 years does the diagnosis occur. This represents potentially a large loss of information, as it could be that certain combinations of risk factors could lead to a much faster diagnosis than other combinations. In addition, if a participant leaves the study early for unknown reasons before being diagnosed (say at 4 years), even for a reason as innocuous as having moved to a better job location, then for purposes of the logistic regression analysis that person either (1) has to have their possible diagnosis imputed via a statistical approach, or (2) is dropped entirely out of the logistic regression analysis, or (3) is quite possibly incorrectly labeled as non-diseased (like anyone else who stayed in the study the entire 10 years without disease), since the person was not diagnosed prior to leaving the study. That is, in approach (3), these individuals are treated exactly the same as someone who stayed the entire study period and had no event, even if they were in the study for a short time period, such as 1 year (vs. 10 years). There are potential problems and concerns with any of these above three approaches to early dropout.

Due to these limitations and concerns above, it is much more informative to use an approach that seamlessly accounts for time under observation in a follow-up study and can specify, as close to as possible, the actual time from the start of a participant's follow-up to the time of disease diagnosis. This is the main reason survival (i.e., time-to-event analysis) techniques are used. One such modeling approach that allows for these accommodations is Cox proportional hazards regression (Cox 1972). As a time-to-event technique, the response we record for proportional hazards regression has two components: (a) how much time was the individual followed in the study, and (b) during that time under observation, did

the individual experience the event, where "event" = Type 2 diabetes diagnosis in the earlier example. In the simplest setting, and one in which we will maintain focus in this chapter, we record the time in "(a)" as the minimum of: (time until the event was observed and time under observation). Hence, if the plan was to follow a person for 10 years, but the person experienced the event in day 737, then the response will be: [(a) 737 days observed, (b) event was experienced]. If, instead, the person remained disease-free over the entire planned follow-up period, the response will be: [(a) 3,652 days (10 years) observed, (b) no event was experienced)]. A final possibility under this scenario is that the person leaves the study before the intended period of follow-up (say, at 840 days) without having yet experienced the event. In this case, the response will be: [(a) 840 days observed, (b) no event was experienced)]. So, even though for both (b) and (c) there are no events recorded, we will explicitly account for the shorter time under observation for the case in (c), something not done in logistic regression.

In summary, there are three outcomes we can record:

(1) we see the person experienced the event at some point during the follow-up period and we record the day of that event,
(2) the person does not leave the study early, but we do not see that the person experienced the event at some point during the entire follow-up period and we record the final day of the follow-up period,
(3) the person does leave the study early before experiencing the event, and we record the final day that we actually observed the person before leaving the study.

Proportional Hazards Model and Assumptions

Outcomes 2 and 3 above are referred to as *right-censored events*, as we assume we would eventually see the event at some point in the future (even with very low probability) had we followed the person for a sufficiently long time period. There is one potential complication we will briefly describe here regarding right-censored events: analyses will require more attention if there is so-called *dependent censoring*, where the censoring date and the fact that the event was not seen are not independent. For example, say a person sees that they are failing to adhere to the advice of the investigators and feels they will soon be diagnosed with Type 2 diabetes. Instead of waiting for this diagnosis, the person leaves the study early, possibly so as not to disappoint the investigators, even though they may seek treatment outside of the scope of the cohort study. This is dependent censoring, and is distinct from the situation where a participant moves from the study area to take a new job, leaving the study early for a reason that has nothing to do with the event of interest; this latter scenario is an example of *independent censoring*. There are means of accounting for dependent censoring at the modeling stage, for example by using appropriate weighting, such as inverse probability of censoring weighting (e.g., Robins and Finkelstein 2000), but we will not delve into this further here

in this chapter. We will move forward under the assumption that censoring we encounter is independent.

In the proportional hazards model, we assume an underlying instantaneous survival rate (i.e., hazard rate), which is generally referred to as the *baseline hazard*; this is the hazard rate for an individual when all covariates/predictors are set to 0. We then model an individual's hazard rate as the multiplicative function of the baseline hazard rate and the exponential of a linear combination of the covariates (or, equivalently, model the logarithm of the hazard rate as an additive function of the logarithm of the baseline hazard and a linear combination of covariates):

$$\begin{aligned} &\lambda_i(t) = \lambda_0(t)\exp(X_i^t\,\beta) \\ &\text{or} \\ &\log(\lambda_i(t)) = \log(\lambda_0(t)) + X_i^t\,\beta. \end{aligned} \tag{18.1}$$

In (18.1), $\lambda_i(t)$ is the individual i's hazard rate at time t, $\lambda_0(t)$ is the baseline hazard rate at time t, X_i is the collection of covariates for individual i (in more generality, we could write $X_i(t)$, representing that at least some covariates are a function of time, i.e., time-dependent), and β is the parameter vector of interest linking the covariates to the hazard rate. One convenient aspect of the proportional hazards model (i.e., 18.1) is that we do not need to specify the explicit functional form of the baseline hazard, other than knowing it is a nonnegative function of time. Also, with the way the proportional hazards model is specified, the hazard rate for an individual will always be nonnegative, a sensible modeling restriction.

As in standard multiple linear regression or logistic regression, each covariate is attached to a parameter, where the sign of the parameter suggests its influence on the hazard rate. So, for example, if a person's BMI is indicative of a faster time-to-event (i.e., a faster log hazard rate), then the parameter associated with BMI will be positive, or the exponential of the parameter (sometimes referred to as the *hazard ratio*) will be greater than 1.0. Alternatively, if a new treatment of interest slowed down the time-to-event (compared to, say, a standard treatment), then the parameter associated with that new treatment would be negative (or the hazard ratio will be smaller than 1.0). Software for running the proportional hazards model is available from R, SAS, Stata, etc.

A key assumption for the proportional hazards model is the assumption that the hazards are proportional (i.e., the aptly named *proportional hazards assumption*). Here, we assume that the hazards rates for two different individuals, each with fixed set of predictors, will be proportional to one another. There are various ways to check on the proportionality assumption, some of the best being graphical. If the assumption is noticeably violated, then some adjustment must be necessary to remove the violation. For example, if gender is the main cause for a violation of proportional hazards, then gender could be used to stratify the model, removing the concern. However, if used for stratification purposes, that predictor can no longer be used to look at the association between that variable and time-to-event.

As with checking on proportional hazards, other assumptions to consider checking include checking the functional form of the model predictors, and the linear form of the right-hand (predictor) side of the model, not to mention the

possibility of dependent censoring. One useful reference for checking proportional hazards and other assumptions in the proportional hazards model is Therneau and Grambsch (2000); this text has a bit of technical detail, but also covers some excellent data analyses and provides very practical suggestions for how to evaluate proportional hazards model assumptions and adjust in case of violations.

The Canadian Study on Health and Aging

In Hall et al. (2009), as discussed earlier in this chapter, a hypothesis involving the possible association between executive function and mortality was investigated from the Canadian Study on Health and Aging (CSHA). We first wanted to look at the survival experience for different strata of intelligence, as measured by full-scale IQ, unadjusted for any consideration of covariates. The strata of IQ compared were lower IQ (i.e., IQ < 85), average IQ (i.e., IQ $= 100$), and higher IQ (i.e., IQ ≥ 115)). This can be viewed in Fig. 18.1.

We can see a separation in the survival curves of these three strata with the trend that higher IQ is associated with longer survival, and, indeed, this result is statistically significant as measured through a log-rank test statistic. But does this result hold up under the scrutiny of adjustment for covariates (i.e., potential confounders) such as age, gender, education, etc.? We used the proportional hazards model to help us assess this, and adjusting for these confounders resulted in the loss of statistical significance regarding the association between full-scale IQ and

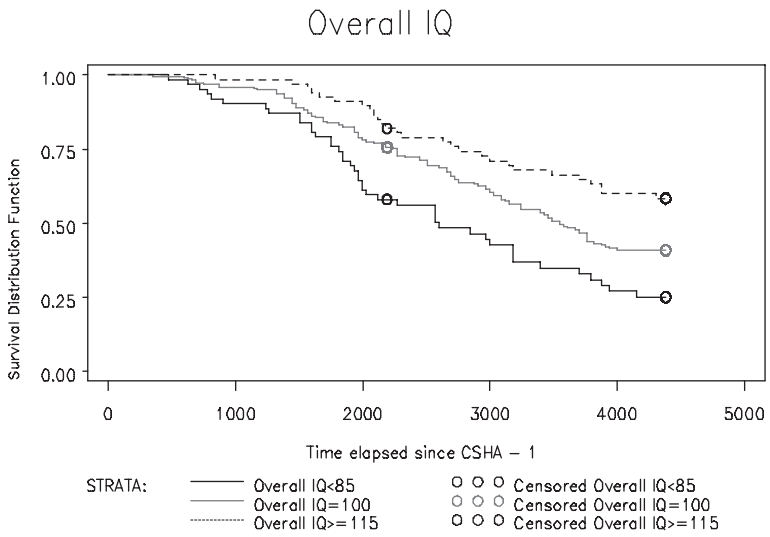

Fig. 18.1 Mortality curve for full scale IQ (reproduced from Hall et al. 2009)

time-to-mortality. First, in Table 18.1, Model 1, we can explicitly view the initial statistically significant association between full-scale IQ and time-to-mortality, without adjustment for confounders. The 95 % hazard ratio confidence interval (0.971, 0.990) is entirely less than 1.0 suggesting lower full-scale IQ is leading to quicker mortality, consistent with Fig. 18.1. However, once covariates are added to the model, we can see this earlier statistically significant association is lost. Model 2 in Table 18.1 shows that when statistically significant confounders age and gender are added to the model, then full-scale IQ no longer maintains its significance, noting 1.0 is now contained in the 95 % confidence interval for the full-scale IQ hazard ratio (0.981, 1.002). And this lack of association does not change when either education (Model 3) or health behavior (Model 4) are added to the model that already contains age and gender.

There was also interest in investigating the association between the components of full-scale IQ and mortality. One such component is the DS executive process. The unadjusted association between three DS score strata and time-to-mortality can be seen in Fig. 18.2. As with full-scale IQ, those with higher DS score tend to survive longer than those with lower DS score, at least when unadjusted for covariates of interest. This is also verified in the unadjusted proportional hazards model; results can be viewed in Table 18.2, Model 1, where we see the entire 95 % confidence interval for the DS hazard ratio to fall below 1.0 (0.959, 0.979).

As opposed to the proportional hazards model for full-scale IQ, where the unadjusted association between IQ and time-to-mortality did not hold after adjustment for important covariates, the association of DS score and time-to-mortality did hold up under a covariate-adjusted (e.g., age, education) proportional hazards model. This can be seen first in Model 2 in Table 18.2, where we fit a proportional hazards model for investigating the association between DS and time-to-mortality, adjusting

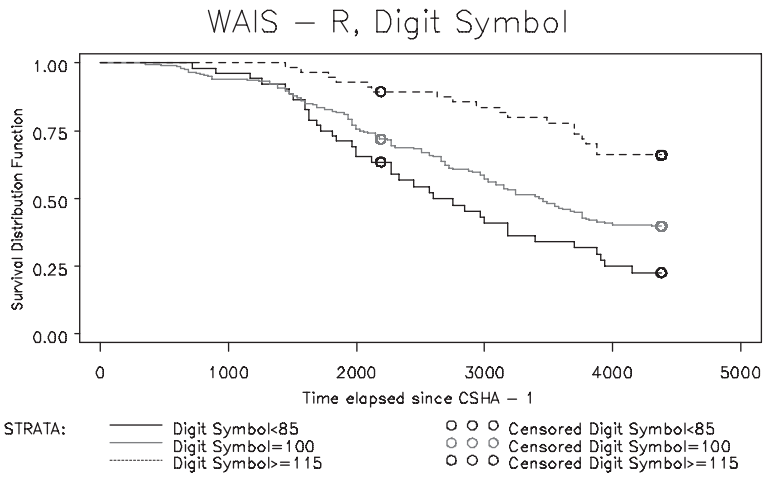

Fig. 18.2 Mortality curve for digit symbol (reproduced from Hall et al. 2009)

Table 18.1 Proportional hazards regression models for full scale IQ (reproduced from Hall et al. 2009)

Covariates	Model 1 ($N = 184$, $n = 163$)				Model 2 ($N = 184$, $n = 163$)			
	Parameter estimate	Hazard ratio	Hazard ratio *CI*	*p* value	Parameter estimate	Hazard ratio	Hazard ratio *CI*	*p* value
Full scale IQ	−0.02001	0.980	(0.971, 0.990)	<0.001	−0.00866	0.991	(0.981, 1.002)	0.099
Age	–	–	–	–	0.10378	1.109	(1.084, 1.136)	<0.001
Gender	–	–	–	–	0.62129	1.861	(1.386, 2.500)	<0.001
Education	–	–	–	–	–	–	–	–
	Model 3 ($N = 184$, $n = 163$)				Model 4 ($N = 92$, $n = 108$)			
Full scale IQ	−0.00813	0.992	(0.979, 1.005)	0.212	−0.01150	0.989	(0.974, 1.003)	0.118
Age	0.10417	1.110	(1.083, 1.137)	<0.001	0.13552	1.145	(1.106, 1.185)	<0.001
Gender	0.61925	1.858	(1.381, 2.499)	<0.001	0.36714	1.444	(0.878, 2.374)	0.148
Education	–0.00310	0.997	(0.953, 1.043)	0.892	–	–	–	–
Health behavior	–	–	–	–	−1.18863	0.305	(0.136, 0.681)	0.004

N number of events, *n* number of censored individuals, *CI* confidence interval

Table 18.2 Proportional hazards regression models for digit symbol (reproduced from Hall et al. 2009)

Covariates	Model 1 ($N = 185$, $n = 163$)				Model 2 ($N = 185$, $n = 163$)			
	Parameter estimate	Hazard ratio	Hazard ratio *CI*	*p* value	Parameter estimate	Hazard ratio	Hazard ratio *CI*	*p* value
Digit symbol	−0.03147	0.969	(0.959, 0.979)	<0.001	−0.01496	0.985	(0.974, 0.996)	0.008
Age	–	–	–	–	0.09682	1.102	(1.076, 1.128)	<0.001
Gender	–	–	–	–	0.55238	1.737	(1.289, 2.343)	<0.001
Education	–	–	–	–	–	–	–	–
	Model 3 ($N = 185$, $n = 163$)				Model 4 ($N = 93$, $n = 108$)			
Digit symbol	−0.01727	0.983	(0.970, 0.996)	0.011	−0.01865	0.982	(0.966, 0.997)	0.019
Age	0.09455	1.099	(1.072, 1.127)	<0.001	0.13016	1.139	(1.100, 1.179)	<0.001
Gender	0.55748	1.746	(1.295, 2.354)	<0.001	0.26276	1.301	(0.787, 2.149)	0.305
Education	0.01340	1.013	(0.970, 1.059)	0.547	–	–	–	–
Health behavior	–	–	–	–	−1.14078	0.320	(0.145, 0.705)	0.005

N number of events, *n* number of censored individuals, *CI* confidence interval

Table 18.3 Proportional hazards regression models for simultaneous entry of WAIS–R subtest scores (digit symbol, block design, comprehension, and similarities)

Covariates	Model 1 ($N = 184$, $n = 163$)				Model 2 ($N = 184$, $n = 163$)			
	Parameter estimate	Hazard ratio	Hazard ratio *CI*	*p* value	Parameter estimate	Hazard ratio	Hazard ratio *CI*	*p* value
Digit symbol	−0.04252	0.958	(0.944, 0.973)	<0.001	−0.02284	0.977	(0.962, 0.993)	0.006
Block design	0.00199	1.002	(0.988, 1.016)	0.774	0.00430	1.004	(0.990, 1.019)	0.564
Comprehension	0.00332	1.003	(0.991, 1.015)	0.587	−0.00101	0.999	(0.987, 1.011)	0.870
Similarities	0.01292	1.013	(1.000, 1.026)	0.051	0.00813	1.008	(0.995, 1.021)	0.215
Age	–	–	–	–	0.09466	1.099	(1.073, 1.127)	<0.001
Gender	–	–	–	–	0.55509	1.742	(1.278, 2.375)	<0.001
Education	–	–	–	–	–	–	–	–
	Model 3 ($N = 184$, $n = 163$)				Model 4 ($N = 92$, $n = 108$)			
Digit symbol	−0.02349	0.977	(0.960, 0.994)	0.007	−0.02399	0.976	(0.955, 0.998)	0.032
Block design	0.00430	1.004	(0.990, 1.019)	0.564	0.01342	1.014	(0.993, 1.035)	0.204
Comprehension	−0.00125	0.999	(0.987, 1.011)	0.842	0.00653	1.007	(0.989, 1.024)	0.464
Similarities	0.00778	1.008	(0.995, 1.021)	0.244	−0.01072	0.989	(0.970, 1.009)	0.288
Age	0.09384	1.098	(1.071, 1.127)	<0.001	0.13501	1.145	(1.103, 1.187)	<0.001
Gender	0.55732	1.746	(1.280, 2.381)	<0.001	0.21256	1.237	(0.740, 2.068)	0.418
Education	0.00583	1.006	(0.961, 1.053)	0.801	–	–	–	–
Health behavior	–	–	–	–	−1.04792	0.351	(0.158, 0.780)	0.010

N number of events, *n* number of censored individuals, *CI* confidence interval

for both gender and age. Though both age and gender are themselves each significantly associated with time-to-mortality, their presence in the model does not remove the statistically significant association between DS and time-to-death [95 % confidence interval for the DS is (0.974, 0.996)]. And, in addition to adjusting for gender and age, if we adjust for either education (Table 18.2, Model 3) or health behavior (Table 18.2, Model 4), the statistically significant association between DS and time-to-death remains. From the specific proportional hazards model that adjusts for age, gender, and education, we were able to detect that a 1-standard deviation difference in DS score performance was associated with a 28 % change in risk of mortality over the 10-year follow-up interval, i.e., a higher DS score at baseline led to a lower risk of mortality, after adjustment of covariates.

In Hall et al. (2009), we also fit two additional proportional hazards models: (1) where both DS and Full Scale IQ were in the model simultaneously, while adjusting for potential confounders age, gender, education and health behavior, and (2) where we have simultaneous entry of all the WAIS-R Subtest Scores, adjusting for the same potential confounders as in (1). In both cases, DS score remained consistently and statistically negatively associated with time-to-mortality (i.e., higher DS scores were associated with statistically significant slower mortality) even in the presence of confounder adjustment. This latter analysis (2) is particularly important, in that it shows that DS—and not any other subtest—is *uniquely* associated with time to mortality. This fairly conclusively demonstrates that global IQ does not predict mortality in the CSHA dataset, but rather a very specific subtest, and that no additional variability is explained by tests assessing other cognitive abilities. This has significant implications for the field of cognitive epidemiology which has largely focussed on the prognostic value of global cognition to the exclusion of considering more specific processes—such as executive function—which may underlie the predictive power of IQ tests for health-related outcomes (Table 18.3).

We should add that for each of the proportional hazards models fit, we investigated potential violations of the assumptions of proportional hazards and linearity, but did not detect any serious violations. There may have been early dropouts that could have resulted in dependent censoring, but we did not have enough detail to draw such a conclusion. That said, as mentioned earlier, there are weighting techniques that can allow for valid model parameter estimates under dependent censoring, and these should be considered when it is clear that dependent censoring exists.

Summary

We have hopefully conveyed the usefulness of the Cox proportional hazards model for follow-up data in public health that has a time-to-event component. This model has several advantages of another popular model in public health that utilizes less information, i.e., the logistic regression model. We described the proportional hazards model and its assumptions, and we demonstrated its usefulness from part

of a national longitudinal study in Canada that looked at the association between executive functioning and time to mortality. We were able to find an important association between DS executive process and time-to-mortality, specifically that higher DS scores are associated with slower time-to-mortality (i.e., longer survival) even after adjustment of strong confounding variables such as age and gender. However, the exact same adjustment for confounding resulted in Full-Scale IQ no longer maintaining its own association with time-to-mortality in a separate model. By describing the analysis goals, the proportional hazards model, and subsequent results from our example, we hope that researchers in social neuroscience and public health will see the utility of analyzing time-to-event data with the proportional hazards model for their own applications.

Highlights

- Survival analysis is part of a more general "time-to-event" approach.
- We describe the most utilized time-to-event regression model, i.e., the Cox proportional hazards model, and state its advantages over another popular model in public health, the logistic regression model. We also describe the assumptions of the model.
- Here we present an example describing an application of survival analysis to predicting mortality from cognitive ability in older adults.
- Survival analyses may be useful in the context of social neuroscience research because of its more complete usage of time-to-event information than some common competing methods.

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Chapter 19
Neurobiological Facets of Food Craving and Consumption: Evidence from Neuropsychological and Transcranial Magnetic Stimulation (TMS) Studies

Cassandra Lowe and Peter A. Hall

Transcranial magnetic stimulation (TMS) is a method for stimulating the cortex of the brain in order to either excite or inhibit a group of neurons, often corresponding with some functional region of interest. TMS has both clinical and research applications, as one might imagine. In the clinical sphere, it has been used as a treatment for depression and substance use disorders. In the research context, it has been used as a means of experimentally inducing activity in motor regions, as well as the prefrontal areas known to be implicated in the control of cognition, emotion, and behavior. In relation to this latter body of research, one area of inquiry has been of particular interest to public health scientists, and that is the evocation (or inhibition) of craving responses to unhealthy—but appetitive—foods. In this chapter, we review the technique (TMS) and the research pertaining to cortical stimulation and craving responses to appetitive foods. We will start with some context for the research question, describe the methodology involved in TMS, and review findings of experimental TMS studies involving taste perception and dietary behavior, with an eye toward public health implications.

Context

Humans have strong preferences for foods that are high in fat and sugar (Drewnowski 1997; Drewnowski and Greenwood 1983). Such preferences are not unique to humans, and have likely been selected for over millions of years of evolution. Given that ancient environments were characterized by relative food scarcity, and that energy must be expended to procure food, the net caloric gain per forage must be maximized in order to ensure survival and likelihood of reproduction. As such, evolution would likely select for food consumptive preferences that result in

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a favorable balance of energy gained per unit of energy expended on procurement. This situation would have stretched from the origin of the species to only a few hundred (or at most, a few thousand) years ago—approximately 98 % of our evolutionary history. Unfortunately, the modern living environment in most developed countries would not be characterized by food scarcity. In fact, the true state of affairs is quite the opposite. In most urban centers (even those of small scale) high calorie food is highly available and convenient to procure. At the same time, very little energy is typically involved in procuring food, given that the food production, packaging, and distribution systems are now highly mechanized. As such, the primary modulating factor of energy intake is the behavior of the individual and the cognitive processes that shape the behavioral choice of what to eat, and how much to consume. To act on preference is tantamount to chronic consumption of high calorie foods that are highly available, with almost no procurement-related energy costs.

Lower calorie and more healthful foods are available, but subject to a number of factors that make their consumption more problematic. First, our evolved preference is for high calorie food tastes, and therefore calorie rich food selections have higher prior probability of occurring; that is, they are the behavioral "default." Second, more healthful foods are less easily available, as they are seldom sold in incidental locations (gas stations, corner stores) or drive-through restaurants. Third, under some circumstances, healthful food is both more expensive to initially purchase and more subject to spoiling (therefore expensive to keep in stock) than more calorie dense processed foods. Finally, our environment is typically saturated with highly salient cues to consume appetitive calorie dense foods via advertising, and therefore availability of such foods in mental representation is high.

Cognitive Control and Dietary Choice

Given the default status of high calorie food selection and consumption, control mechanisms could be implicated in the avoidance of such behavioral tendencies. Indeed there are some studies that have indicated that stronger executive control resources (ECRs) are associated with less frequent consumption of fatty foods (Hall 2012; Nederkoorn et al. 2010), and such resources also moderate the intention-behavior link for dietary behavior (Hall et al. 2008). Given that ECRs are understood to centrally involve the operation of the prefrontal cortex (Miller and Cohen 2001), it is possible that operation of the PFC drives successful self-initiated self-regulatory processes in eating behavior. The existing observational studies seem to be consistent with this proposition. However, in order to make more firm statements about the causal primacy of ECRs in dietary behavior, one must be able to manipulate ECRs—via the brain structures that underlie them—and observe the subsequent effect of such manipulation on experienced cravings and dietary behavior. Such investigations could rely on a few specific techniques for acutely manipulating cortical function using TMS. We review the TMS methodology in detail below.

TMS

One promising laboratory technique for modulation of cognitive control resources is TMS. The basic TMS apparatus (Fig. 19.1) consists of a wire coil that is placed directly on the scalp (Fig. 19.2). To permit focal stimulation, two circular coils are combined to form a figure eight (Wassermann and Zimmermann 2011; Sandrini et al. 2011). The coil emits electromagnetic pulses—of varying length, form, and intensity—that induce changes in cortical excitability (upwards or downwards); this modulation of excitability can increase or decrease activity in the cortical region below the area of application. From a scientific perspective, TMS is of interest because it is a noninvasive tool that provides researchers the unique opportunity to interfere with neural activity in specific brain regions with high temporal (i.e., time course) and regional (i.e., brain region) precision (Allen et al. 2007; Wassermann and Zimmermann 2011; Sandrini et al. 2011). Unlike other methodologies, TMS allows researchers to map brain function in a cognitively intact human population, rather than relying on animal models, neurosurgical procedures, or patients with focal brain lesions (Pascual-Leone et al. 1999). Additionally, using TMS on healthy populations allows researchers to map brain functions while avoiding the confounds associated with uncontrollable brain lesions or the reorganization of brain function, which may occur in the event of a brain lesion (Pascual-Leone et al. 1999).

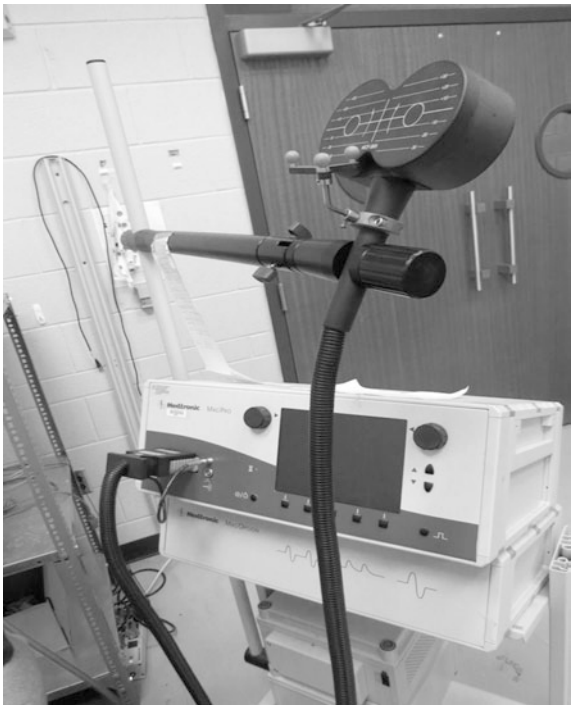

Fig. 19.1 The TMS apparatus

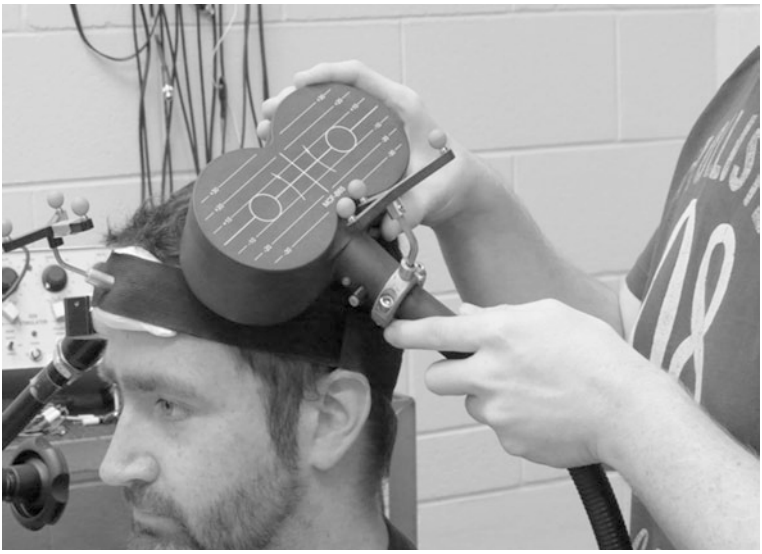

Fig. 19.2 The TMS coil is placed directly on the participant's scalp, and the coil is placed in such a way that the focal point (i.e., the cortical area being stimulated) is situated directly under the middle of the coil

For example, decreasing cortical excitability in a specific brain region creates a reversible "lesion", thus researchers can measure changes in cognitive and physiological processes related to the deactivation of a specific brain region. Conversely, researchers can increase cortical excitability to determine how the activation of a specific brain region influences cognitive and physiological processes. In addition, TMS studies can be conducted across multiple participants (i.e., between subjects designs) and can be repeated on the same participant multiple times (i.e., within subjects designs) thus allowing researchers to infer a causal relationship between focal brain activity and subsequent behavior (Pascual-Leone et al. 1999).

Types of TMS

TMS can be applied as a single pulse (spTMS) or a repetitive train of pulses (rTMS) (Sandrini et al. 2011). The duration of spTMS is less than 1 ms, whereas the duration of rTMS can typically span between 10 and 25 min (Anand and Hotson 2002; Sandrini et al. 2011). The type of TMS paradigm used depends on the brain-behavior relation being investigated. Single pulses of TMS are effective for producing short responses, and are usually used to measure muscle movements; spTMS-induced neuronal changes only last for approximately 40–60 ms (Sandrini et al. 2011), which is sufficient for studying motor movements (Wassermann and Zimmermann 2011).

Stimulation and task performance must occur concurrently when using spTMS paradigm (Sandrini et al. 2011). For example, a single pulse of TMS to the primary motor cortex (M1) evokes immediate muscle activity (motor evoked potential (MEP)), which can be measured using electromyogram (EMG) (Wassermann and Zimmermann 2011). Given that single pulse TMS is effective at producing short-term responses, it is ideal for measuring immediate behavioral effects; however, spTMS is not as effective as rTMS at investigating how cortical stimulation can affect higher order cognitive processing (e.g., language or memory) (Sandrini et al. 2011; Ridding and Rothwell 2007; Anand and Hotson 2002). In rTMS, a train of pulses is delivered at a frequency up to 50 Hz, which can evoke sustained neural activity (after effects), thus allowing researchers to examine cognitive functions that are not affected by spTMS (Anand and Hotson 2002; Wassermann 1998). The duration of rTMS after effects can range between 30 and 60 min, depending on the number of pulses applied, the rate of application and the stimulus intensity (Ridding and Rothwell 2007). Generally speaking, stimulation frequencies higher than 1 Hz tend to cause facilitatory aftereffects by increasing cortical excitability (Ridding and Rothwell 2007; Sandrini et al. 2011). Conversely, stimulation frequencies lower than 1 Hz tends to produce an inhibitory aftereffect by decreasing cortical excitability (Ridding and Rothwell 2007; Sandrini et al. 2011). Because of the more durable effects of rTMS, it is likely to be most useful type of TMS for investigations involving cortical modulation and subsequent dietary behavior, given that such behavior is not likely to be simultaneous with the stimulation.

Theta burst stimulation (TBS) is a variant of rTMS in which consists of three short pulses (between 50 and 100 Hz) that are repeated every 200 ms (5 Hz; Huang et al. 2005; Oberman et al. 2011). The parameters for TBS were designed to mimic theta rhythms, which are associated with a phenomenon known as "long-term potentiation," or enhancement in signal transmission between nerve cells (Oberman et al. 2011). There are two types of TBS, continuous TBS (cTBS) and intermittent TBS (iTBS; Huang et al. 2005; Oberman et al. 2011). In cTBS, the pulses are applied at a rate of 5 Hz for either 20 s (100 bursts) or 40 s (200 bursts), resulting in an inhibitory effect (Huang et al. 2005; Oberman et al. 2011). Conversely, in iTBS the pulses are applied at a rate of 0.1 Hz in 2 s intervals, resulting in a facilitating effect (Huang et al. 2005; Oberman et al. 2011). Since TBS can be administered in a shorter time interval and is considered to be more efficient than other forms of rTMS, TBS is becoming the preferred method of administering rTMS (Oberman et al. 2011).

Within experimental approaches to public health science, TMS holds promise as a method for manipulating cortical function in the laboratory to observe causal effects on health-related behaviors that rely on self-control. To date, TMS has been used to a limited extent only, despite its potential for uncovering causal brain-behavior effects that are of interest to public health researchers. One of the more interesting such applications is the use of TMS to examine the causal impact of prefrontal cortex function on food cravings and food choice behaviors. To date several investigations have been undertaken, and these are summarized in the next section.

Cognitive Control, Food Cravings, and Dietary Behavior

Healthy dietary patterns require planning and the ability to overcome the temptation of high calorie fatty foods. Individuals with low ECR may lack the inhibitory control needed to resist fatty foods and the capacity to plan and execute healthy food choices. The existing observational literature is in line with this proposition. For instance, when presented with high calorie foods, individuals with weaker inhibitory control are more likely to consume more food than their counterparts (Guerrieri et al. 2007; Houben 2011). Allan et al. (2011) reported that inhibitory control was related to the consumption of fruit and vegetables and the avoidance of snack foods. Participants with higher scores on measures of planning, switching, and flexibility were more likely to eat their intended amount of fruit and vegetables, whereas, individuals with lower inhibitory control were more likely to consume more snack foods. Allan et al. (2010) reported that in participants who intended to avoid snack foods, performance on a Stroop task (measure of inhibitory control) can account for 23 % of the variance in the amount of chocolate consumed in a bogus taste test. A lower level of inhibitory control was associated with more unintentional eating (consuming more chocolate) and a higher BMI. A recent study by Hall (2012) using an age stratified community sample showed the ECRs consistently (and selectively) predict more frequency fatty food consumption, and this effect is largely invariant across age groups from young adulthood to older adulthood.

Research in populations that typically overeat has consistently shown that both overweight and obese adults and children have weak ECRs, specifically heightened impulsivity and lower inhibitory control (Braet et al. 2007; Cserjesi et al. 2009; Gunstad et al. 2007; Guerrieri et al. 2008; Nederkoorn et al. 2006). An increasing body of evidence suggests that the dorsolateral prefrontal cortex (DLPFC), a brain region associated with ECRs (such as inhibitory control), may play a role in regulating food craving and dietary behaviors (Barth et al. 2011; Fregni et al. 2008). For example, after a meal, obese men and women have significantly less activation of the DLPFC than their normal weight counterparts (Le et al. 2006, 2007). In a recent study by Hare et al. (2009), the neural activity of self-described dieters was measured while the participants choose which foods they would like to eat. Individuals with higher self control made decisions on which foods they would like to eat on the basis of a combination of health considerations and taste, whereas, individuals with low self control made decisions based on taste alone. In addition, participants with high self-control choose not to eat the tasty but unhealthy foods more often than those with low self- control. Regardless of the degree of self-control, regions of the ventral medial prefrontal cortex (vmPFC) were activated when making decisions about which foods to eat, whereas, an increase in the left DLFPC is observed only in participants with high self-control, suggesting that the DLPFC may be important for regulating food intake and inhibitory control. The vmPFC is typically associated with the short-term value of a given stimuli whereas the DLPFC is required for higher order

cognitive functions. Individual differences in the connectivity between the DLPFC and vmPFC or the degree in which the DLPFC can modulate the vmPFC might explain individual differences in dietary behaviors (Hare et al. 2009).

Experimental designs are necessary for inferring causal primacy to PFC function in driving eating behaviors, and cortical stimulation paradigms may provide that. Currently, there are only a few such studies in existence.

Review of the Cortical Stimulation Literature

Uher et al. (2005) reported that high-frequency (10 Hz) rTMs to the left DLPFC decreased food cravings in women when compared to sham rTMS. Participants were preselected based upon self-reported frequent, "very strong" or "strong" urges to eat at least one of the unhealthy snack foods and assigned to receive either active or sham rTMS. Before and after the TMS session, participants underwent a food exposure session, in which they were required to rate the food on taste, smell, appearance, and their current urge to eat. Food cravings in the active rTMS group remained constant across pre- and post-food exposure sessions, whereas post-food exposure cravings significantly increased in the sham rTMS group. Because participants were given the opportunity to taste, smell, and inspect the foods before and after rTMS, it was posited that the increase in food cravings during sham rTMS treatment can be attributed a cue-reactivity effect. Therefore, active rTMS stimulation to the left DLPFC was able to decrease food cravings, thereby downregulating the usual craving response. However, the authors reported that there was no significant difference in food consumption between active and sham rTMS groups, indicating that active rTMS had no effect on regulating food consumption in this case per se.

Consistent with the results of Uher and colleagues, Fregni et al. (2008) found that transcranial direct current stimulation (tDCS) to the left DLFPC significantly reduced food cravings. Participants were again preselected based upon frequent food cravings. In this study, participants received three different types of tDCS to the DLPFC: (1) active anode left/cathode right; (2) active anode right/cathode left; (3) sham tDCS. Using a methodology similar to Uher et al. (2005), participants underwent food exposure before and after tDCS, in which they were required to rate the food on taste, smell, appearance, and their current urge to eat. In addition, participants were shown a 5-min movie that was designed to elicit food cravings. As a secondary measure of food cravings, participants were required to look at slides of different foods. Each slide contained four different pictures, with only one of the pictures being a food picture. Using an eye tracker device, the authors also measured the fixation time and number of fixations on pictures of foods associated with cravings.

After active anode right/cathode left tDCS there was a significant decrease in the fixation time on the food picture, whereas there was a significant increase in fixation time after sham tDCS. Active anode right/cathode left stimulation of the DLPFC significantly decreased food cravings, whereas there was no change

in food cravings after active anode left/cathode right tDCS. There was a significant increase in food cravings after sham tDCS. Although, there were no significant differences in food cravings between anode right/cathode left and anode left/cathode right DLPFC stimulation, anodal right and anodal left stimulation of the DLFPC had differential effects on food cravings, suggesting there might a hemispheric laterality for food cravings (Fregni et al. 2008). The left and right DLPFC may play different roles in regulating food cravings; the right DLPFC might suppress desire to eat altogether, thus decreasing food cravings, whereas the left DLPFC might regulate cravings or function as the neural mechanism needed to suppress food cravings (Fregni et al. 2008). In contrast to the results reported by Uher et al. (2005), Fregni et al. (2008) reported a decrease in the caloric content of food consumed after active tDCS (both conditions) compared to sham tDCS., which may be due to hemispheric laterality differences. However, in a subsequent study by Goldman et al. (2011), there was no significant difference in the amount of food consumed between active right DLPFC stimulation and sham tDCS sessions, highlighting the current uncertain state of the literature with respect to consumptive behavior.

Goldman et al. (2011) showed participants pictures of foods that typically elicit cravings before and after tDCS treatment. Similar to the studies described above, participants were preselected based upon frequent food cravings. While viewing the images participants rated how much they would like to eat the food (cravings), liked the food, and if they would be able to resist tasting the food. The authors found that the self-reported ability to resist food cravings, among individuals who had frequent food cravings, was significantly higher after active anodal right tDCS to the DLPFC compared to sham tDCS. Overall, the data summarized above support the conclusion that selective activation of the DLPFC has an effect on food cravings.

Finally, contrary to prior research, Barth et al. (2011) reported that food cravings were significantly decreased in both the real and sham rTMS conditions. The authors propose that because the sham condition produced a similar amount of pain as the real rTMS, emotional reaction to the painful procedure may have caused the inhibition of food cravings. One important methodological difference between Barth et al. (2011) study and other studies described above is the absence of preexposure to the food. This methodological difference may also have influenced the null findings between groups, as the appetitive response to the food may not have been effectively induced in either group. It is also important to point out that, although tDCS is a cortical stimulation technique, it does differ from TMS as it can induce uncomfortable physical sensations that might influence responsivity to experimental arrangements (as could have been the case in the Barth and colleagues study).

Summary and Future Directions

Most (but not all) prior research studies have demonstrated that stimulation of the DLPFC (via rTMS or tDCS) can reduce cravings for appetitive (but unhealthy) foods among those who report frequent experience of such cravings. These findings

are consistent with a number of other studies involving TMS that have shown, that modulation of the DLPFC results in decreased cravings for other appetitive substances, including cigarettes among current smokers (Johann et al. 2003; Amiaz et al. 2009; Eichhammer et al. 2003; Fregni et al. 2008), alcohol (Boggio et al. 2008) and cocaine (Camprodon et al. 2007). ECR, and the brain regions that support them, appear to be implicated in the control of cravings, based on existing cortical stimulation studies.

The findings regarding observed consumption of appetitive foods is less clear however. In three studies described involving dietary behavior, participants were given the opportunity to consume a variety of fatty high calorie foods. Fregni et al. (2008) reported that participants consumed less food after active tDCS compared to sham tDCS. However, Uher et al. (2005) and Goldman et al. (2011) reported that there was no significant difference in the amount food consumed between active and sham TMS sessions. Some of the possible reasons why such heterogeneity of findings exists in the food consumption domain may have to do with the participant selection procedures, which does not always ensure equal representation of body composition among participants (some of whom may experience stronger cravings than others). In addition, most existing studies are necessarily small in sample size, and observed power calculations are rare; due to the latter, we do not know if the effect does not exist, or the sample size was too small to detect it. In any case, the uniformity of effects in favor of a causal role of DLPFC in food craving generation is encouraging, and supports the contention that the function of the DLPFC may modulate upstream precursors of intake when appetitive foods are involved.

Nonetheless, there is clearly more room for new experimental studies on prefrontal function and dietary behaviors. For example, there are no existing studies that directly measure changes in ECRs as a result of TMS activation of the DLPFC (such changes are only inferred based on the placement of the coils; the "manipulation check" itself is not typically performed). Future research should examine changes in ECRs as a result of the stimulation of the DLPFC, and whether these mediate effects on either craving or food consumption. Such methodological advancements would help to more clearly explore the causal link between cortical function and dietary behavior in relation to appetitive (but unhealthy) foods.

Perhaps of larger significance to the field of public health is the potential utility of TMS research for examining the causal effects of cortical function for dietary behaviors. For a long time, it has been assumed that only the magnitude of the impulse to consume varied, and such impulsive tendencies fully determine differences in susceptibility to weight gain and obesity. We now have a more nuanced understanding of the brain and the relation between control systems and such impulsive systems (Hall and Fong 2013; Hofmann and Van Dillen 2012). TMS allows us to only influence cortical systems, which largely excludes the deeper structures implicated in the generation of impulses themselves (i.e., the dopamine modulated systems in older brain structures). We know that the net effect of even cravings themselves—regardless of manifest eating behavior—can be modulated by the dorsolateral regions of the prefrontal cortex, and such effects could be important for understanding responses to cues in the everyday environment (e.g., advertisements for appetitive foods on televisions, billboards or at important points of food purchase). As such, TMS may play a crucial role in

investigation of the effects of media messaging/imaging on consumptive behavior. Collaboration between cognitive neuroscientists with expertise in TMS and public health scientists who have interest in causal determinants of dietary behavior, and responses to consumptive cues, could be very fruitful indeed.

Highlights

- TMS is a method for inducing temporary modulations of cortical function.
- TMS studies have demonstrated that the prefrontal cortex is involved in the modulation of food cravings.
- Such findings complement findings from observational studies linking executive control with consumption of appetitive foods.
- Future collaborations between cognitive neuroscientists and public health scientists may help to uncover causal linkages between food advertising exposure, cognitive control, and consumptive behavior.

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