

RUNNING HEAD: NEURAL PREDICTORS OF ADDICTION

Functional neural predictors of addiction outcomes

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Abstract

An emerging approach in the addiction literature is to use neuroscientific data to predict addiction-related outcomes (e.g., relapse). Studies using this approach are grounded in process-level models of addiction, and thus leverage neuroscientific knowledge and methods about those presumptive processes to gain explanatory power that would otherwise remain elusive. For example, neural activation during basic inhibitory control and conflict resolution tasks predicts success and failure during attempts to quit smoking and drinking alcohol, above and beyond task performance and other standard measures of risk. In this chapter, I review studies that use functional neuroimaging to predict outcomes related to nicotine, alcohol, and drug use as well as food intake. I also identify several conceptual considerations in using the approach and directions for its future growth.

Keywords: addiction, prediction, brain-as-predictor, functional neuroimaging, nicotine, alcohol, methamphetamine, cocaine, food, craving

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The challenge of predicting addiction outcomes

There has been tremendous public investment in addiction research over the last decades. The National Institutes of Health alone spent between \$1.5 and \$2 billion on substance research in each of the past five years (NIH, 2014). Despite the progress that has been made in many areas of addiction research—most notably in understanding the neurobiological systems of addiction and developing “personalized medicine” treatments—the availability of valid and reliable tools to predict individual differences in substance use and addiction onset, relapse, and treatment response remains limited. For the most part, the best predictors of these addiction-related outcomes are the same ones we knew about ten or twenty or even fifty years ago, including stress and negative affect (Preston & Epstein, 2011; Sinha, 2001), drug craving and urges (Epstein, Willner-Reid, Vahabzadeh, Mezghanni, Lin, & Preston, 2009; Shiffman, 2005), and sociodemographic, familial, and personal history factors (Fergusson, Boden, & Horwood, 2008; von Sydow, Lieb, Pfister, Höfler, & Wittchen, 2002). A notable exception to this trend is genetic markers for addiction, which in recent years have been identified for a range of substances including alcohol, cocaine, heroin, and nicotine (Li & Burmeister, 2009) and phases of the addiction process (Amos, Spitz, & Cinciripini, 2010). Nonetheless, there is still considerable variance in addiction-related outcomes left unexplained even by genetic, social, and personal factors (Sinha, 2011). We can do better.

In this chapter, I describe a new frontier in this area of addiction research: the use of neuroimaging to predict addiction outcomes. Much like the genetic approach that shortly preceded it, a central goal of the neuroimaging approach is to incrementally improve knowledge and tools that will help chip away at the problems of predicting addiction onset, progression, and treatment outcomes for a given individual. The approach leverages many of the neuroscientific

advances described throughout this volume, though is characterized by a particular focus on *prospective prediction* rather than biological description. I will begin by describing the background and history of the neural prediction approach and outline some of its unique challenges and advantages. Next, I will briefly review a number of promising studies that illustrate this approach in the areas of addiction to nicotine, illicit substances, alcohol, and food. Following the review, I will step back from the empirical literature to gain perspective on some important conceptual issues that emerge from the first few years of studies using the neural predictors of addiction. Finally, I'll close with a brief discussion of where I think the neuroscience of prediction is headed in the future. For now, however, I begin with its origins.

The promises and pitfalls of using neuroimaging for prediction

The high degree of enthusiasm for neuroscience generally and neuroimaging particularly in the last decade is reflected in the breathless subtitles of popular books such as “How Neuroscience Can Empower (and Inspire) Marketing” (Van Praet, 2012), “The New Brain Science of Contentment, Calm, and Confidence” (Hanson, 2013), and even, “How to Rewire Your Brain and Create Your Dream Life” (Dalgliesh, 2014). Predictably, the unbridled advocacy for neuroscience embraced by these books has sparked a backlash comprised of books with equally colorful subtitles including “The Seductive Appeal of Mindless Neuroscience” (Satel & Lilienfeld, 2013), “What Neuroscience Can and Cannot Tell Us About Ourselves” (Burton, 2013), and “On the Limits of Brain Science” (Legrenzi, Umiltà, & Anderson, 2011), which have begun to overtake the first kind of book on the bestseller lists. This back and forth illustrates, in part, the natural intellectual lifecycle of any new science technologies (over-optimism followed by over-skepticism and eventually cautious acceptance), and, more specific to the present case,

the importance of clearly thinking through the utility of neuroimaging above and beyond any existing, and perhaps lower-cost, technologies.

So what can neuroimaging tell us about addiction outcomes? Perhaps this question is best answered after a first, more skeptical one is addressed: Why would we expect neuroimaging to tell us anything that we wouldn't be able to discover without it? In the last few years, my colleagues and I have proposed a taxonomy of answers to that question (e.g., Berkman & Falk, 2013). One class of answers includes ways that neuroimaging can directly predict addiction outcomes per se (e.g., risk of onset or likelihood of relapse), which I'll call *primary prediction*. The other class uses neuroimaging to provide ancillary information about moderators of addiction outcomes (e.g., factors that contribute to the likelihood of response to a given intervention), which I'll call *secondary prediction*. Throughout, I refer to neuroimaging as a class of several imaging modalities including magnetic resonance, electroencephalography (EEG), and transcranial stimulation, but the majority of the studies discussed here use functional magnetic resonance imaging, or fMRI.

There are three main reasons to believe that neuroimaging might have utility for primary prediction. First, it has the ability to circumvent introspective biases inherent to direct report because it doesn't require participants to have insight into (or even the ability to report upon) their own motives, behaviors, and attitudes, which they often lack (Nisbett & Wilson, 1977). If a substance is particularly tempting to a person—even if he or she is unaware of that fact—that relatively high temptation might be evident in a rank-ordering of neural activity across a group of otherwise similar participants. Second, it is possible that small or subtle differences between individuals in a mental process, which could cumulatively affect behavior in the long term, are not detectable by other methods that assess the mental process less directly than neuroimaging.

Drawing an example from the clinical literature, neuroimaging during emotional processing is predictive of cognitive behavioral therapy (CBT) treatment response in depression above and beyond other measures (Siegle, Carter, & Thase, 2006) and CBT has specific effects on activity in emotional processing regions during positive versus negative stimulus viewing that are associated with symptom change (Yoshimura, Okamoto, Onoda, Matsunaga, Okada, Kunisato, et al., 2014). In these cases, it may be that neuroimaging is able to predict treatment outcomes because it is sensitive to relatively subtle processes (e.g., emotional reactivity) that are difficult to gauge with other measures. Third, neuroimaging has the ability to measure simultaneously multiple neurocognitive processes and the connectivity among them, which may contain critical information about addiction outcomes even in the absence of observable behavioral differences. For instance, early life stress (which, incidentally, is itself a risk factor for a range of addiction outcomes; Sinha, 2008) is reflected not in emotional reactivity or emotion regulation, but rather in the pattern of connectivity among brain regions associated with them (Taylor, Eisenberger, Saxbe, Lehman, & Lieberman, 2006). The ability of neuroimaging to assess multiple ongoing processes at once may be particularly useful in predicting outcomes related to addiction, which are often cast in terms of interacting psychological processes (e.g., Redish, Jenson, Johnson, & Kurth-Nelson, 2007).

There are also several good reasons why neuroimaging might be useful for secondary prediction, or the prediction of moderating, protective, or risk factors. One is that neuroimaging can sometimes reveal surprising information about the brain regions involved in a given process, which might in turn steer the field toward research questions that it may not have asked otherwise. In one case, the finding that activity in a brain region associated with *affective meaning* during quit-smoking message exposure predicted later treatment-seeking led

researchers to explore the role that process plays in behavior change, even though affective meaning is not part of traditional theories of persuasion (Falk, Berkman, & Lieberman, 2012). Another kind of secondary prediction involves individual or group differences in key moderators of addiction-related outcomes. For example, neural responses to an episode of social rejection can prospectively predict depression onset among adolescents (Masten, Eisenberger, Borofsky, McNealy, Pfeifer, & Dapretto, 2011); given that depression and deviant peer influence are risk factors for substance use among young people, neural responses to rejection and other social processes might provide information about who is more or less likely to develop addiction in a peer context. More broadly, neuroimaging may help identify sensitivities, vulnerabilities, and other potential points of influence where contextual, cultural, or genetic factors may eventually seep in and lead to, or protect against, substance use and addiction.

A realistic assessment of the promise of neuroimaging for prediction must be balanced by a clear-eyed acknowledgment of its limitations. The most obvious among these is cost: neuroimaging with magnetic resonance can cost anywhere from \$300 to \$1000 per hour, and adequately powered studies typically require at least 30 participant hours—and perhaps twice as many for bona fide prediction studies (see below for further details on this issue). This constraint should trigger an opportunity cost calculation at any time, and particularly so in the current climate of scarce research funding. At least, researchers can and should consider whether there is a way of obtaining the same information without using such a costly method. The other major limitations are statistical and interpretational in nature. Statistically, building valid prediction models is not trivial (see Stone, 1974, for a discussion of this issue) and often requires gathering separate “training” and “test” datasets to separately build the model and independently verify it. Interpretively, prediction models generally lack a clear psychological explanation. Activation in

region X may predict outcome Y quite well, but the reason for why is nearly always obscured. This limitation is closely linked to the reverse inference fallacy in neuroimaging (Poldrack, 2006) that a given neural activation can be attributed to a specific mental process. Because the mapping between brain regions/systems and mental processes is many-to-many, the ability to infer a specific mental process from an observed pattern of data is always probabilistic and never certain. I have described this issue elsewhere in terms of a trade-off between predictive validity and explanatory specificity (Berkman & Falk, 2013), where the former is gained at the expense of the latter, and will return to it in subsequent sections of this chapter.

Despite these limitations, or perhaps in recognition of them, I now turn to practical examples where the “brain-as-predictor” has been applied fruitfully to several areas of addiction. Work in this area is active but still emerging, so I will focus here on the types of addiction that have garnered the most empirical attention: nicotine and tobacco intake, alcohol use and abuse, illicit drug use and abuse, and energy-dense food intake.

Predicting addiction outcomes with neuroimaging: Empirical examples

Nicotine and tobacco

In one of the first lines of research to use neuroimaging to predict addiction outcomes, my colleague Emily Falk and I ran a series of conceptually-related studies to explore the potential utility of the approach in the cigarette smoking cessation domain. There are important differences across the studies, but from a distance they all conform to a two-step structure: a first step in which fMRI data are gathered about a neurocognitive process that is hypothesized to be involved in the outcome under investigation, and then a second step in which non-neuroimaging data on the outcome are gathered and predicted (in a statistical sense) from the fMRI data. This is not the only way to structure a neural prediction study, but the essential ingredients are a brain-

based predictor variable, an addiction-related outcome variable, and the minimal amount of time separating the two to make the prediction hypothesis non-trivial. A bonus feature of any neural predictor study is some information about what the prediction accuracy would have been without the neural data (e.g., inclusion of standard self-report or task-based measures; Berkman & Falk, 2013).

We began this line of work by testing whether the ability to engage a specific neurocognitive processes, response inhibition, which is typically assumed to be involved in smoking cessation, is indeed predictive of cessation outcomes (Berkman, Falk, & Lieberman, 2011). Response inhibition was operationalized as functional activation in three regions within the inhibitory control network—the right inferior frontal gyrus (rIFG), the basal ganglia (BG), and the presupplementary motor area (preSMA)—during a stock Go/No-go task (Chikazoe, Konishi, Asari, Jimura, & Miyashita, 2007) in a sample of cigarette smokers who intended to quit in the coming weeks. We chose this task specifically because there is a high degree of consensus in the field that it taps response inhibition and because the pattern of neural activity it elicits is well established. In other words, we used this task to index a known neurocognitive response in our particular sample. (I note that this is at odds with one standard approach in cognitive neuroscience, which is to map the unexplored functional architecture of a process in a way that will be generalizable to some population of interest; I will return to this difference in the concluding section.) Subsequent to the scan, the participants initiated their quit attempt and we monitored their progress for three weeks using automated text messaging. Throughout that period, participants reported their current craving and two-hour past smoking eight times each day. We then built multilevel models of these data to predict smoking at time i based on cravings from time $i-1$ (controlling for smoking at time $i-1$ and craving at time i), and allowed neural

activation to moderate that relationship—between cravings at one time point and smoking at the next.

The data revealed that the lab-based index of response inhibition derived from neuroimaging of the Go/No-Go task meaningfully related to response inhibition in the real-world context of cigarette smoking cessation. People who had higher activation in three regions of the inhibitory control network (rIFG, BG, and preSMA) had an attenuated link between craving and later smoking during an actual quit attempt; people with the lowest activation in those regions showed the strongest craving-smoking relationship in daily life. Performance on the task did not relate to any smoking-related parameter in the model. We were somewhat surprised by these initial results given the seemingly large conceptual distance between the Go/No-Go task (which, for the uninitiated, is like playing a video game that is in equal measure boring and frustrating) and in vivo self-regulation of cigarette craving. The most direct interpretation is that the neural activation contains unique information about a stable component of response inhibition ability above and beyond the behavioral measures derived from the task.

INSERT TABLE 1 AROUND HERE

The next two studies in this line of work focused on persuasive health messaging as a key process in cigarette smoking cessation, and adopted a similar two-step approach. We acquired neuroimaging data while the sample of smokers from the study above viewed a series of 30-second professionally developed quitting ads (Falk, Berkman, Whalen, & Lieberman, 2011). Putting together the theory that self-relevance increases persuasion (Petty & Cacioppo, 1979; 1990) and the evidence that activity in the medial prefrontal cortex (mPFC) tracks self-relevance (Moran, Heatherton, & Kelley, 2009), we reasoned that activity in the mPFC during exposure to these ads would predict smoking cessation (as measured by exhaled carbon monoxide) at least as

well as traditional self-report measures of persuasion. Indeed, activity in an a priori area of the mPFC predicted subsequent reductions in smoking even when controlling for self-report measures of intentions to change, perceived efficacy of the ads, and the self-relatedness of the ads (Falk et al., 2011). A study from another group replicated this finding (Chua, Ho, Jasinska, Polk, Welsh, Liberzon, et al., 2011). More importantly, the degree of mPFC activity elicited by the ads in our sample predicted the population-level effectiveness of those ads—and did so better than all self-report measures—when the ads were later deployed in various states around the country as indexed by the pre-to-post deployment change in 1-800-QUIT-NOW hotline call volumes (Falk et al., 2012). Together, these studies provide strong support for the idea that functional brain activation contains information about the persuasiveness of health messaging that is difficult or impossible to access through traditional self-report means.

It is also feasible to predict nicotine-related outcomes using neural activity related to basic neurocognitive processes such as reward responsiveness. For example, differential neural activity in the anterior insula while simply viewing smoking-related (vs. non-smoking related) images predicts an increased likelihood of “slips” during a cessation attempt (Janes, Pizzagalli, Richardt, Frederick, Chuzi, Pachas, et al., 2010). Several studies have taken this idea one step further based on the ideas that addiction diminishes reward responses to non-abused substances as it also increases reward responses to abused ones (Koob & Volkow, 2010) and that addiction severity is indexed by the difference in the neural response between the two types of rewards. For instance, Versace and his colleagues have shown using electroencephalography (Versace, Lam, Engelmann, Robinson, Minnix, Brown, et al., 2011) and fMRI (Versace, Engelmann, Robinson, Jackson, Green, Lam, et al., 2014) that the relative difference in activity between smoking and non-smoking cues in reward and visual processing regions is predictive of

subsequent relapse and other difficulties with cessation. Similarly, nicotine deprived smokers who showed less activation in the ventral striatum (VS) to monetary rewards compared to their peers were the least likely to be willing to attempt to abstain from smoking (Wilson, Delgado, McKee, Grigson, MacLean, Nichols, et al., 2014). This reduced VS response to monetary rewards among abstinent smokers also predicted a greater sensitivity of the valuation system to cigarette accessibility; smokers who had a diminished reward response at baseline tended to devalue non-cigarette rewards when cigarettes were available, whereas smokers with a higher baseline reward response showed no effect of availability (Wilson, Smyth, & McLean, 2014). These last two studies in particular suggest a very specific risk pathway for the maintenance of nicotine addiction: devaluation of alternative nondrug rewards in the (real or perceived) presence of nicotine. Though research on this topic is only beginning to gain traction, combining fMRI with methods that allow a more nuanced assessment of everyday experience such as ecological momentary assessment (EMA; Shiffman, Stone, & Hufford, 2008) has already proven to be a generative approach for theoretical and process-level insights (see also Wilson et al., 2014b).

Illicit drug use and abuse

Functional neural activation has also been shown to be prospectively predictive of onset, maintenance, and abstinence of use of illicit drugs including cannabis, cocaine, and methamphetamines. Many of these studies have focused on basic neurocognitive processes because of their putative role in addiction (Goldstein & Volkow, 2002, 2011; Noel, Brevers, & Bechara, 2013). In perhaps the earliest illustration of the approach, Paulus and colleagues (2005) used neural activity during decision making to predict relapse among treatment seeking methamphetamine users. They found that activity in several regions including the insula, inferior parietal lobule, middle temporal gyrus, cingulate, and—interestingly—VS reliably distinguished

between individuals who relapsed and those who did not. And, as in the studies reviewed above on nondrug reward reactivity predicting smoking cessation outcomes, methamphetamine users who showed greater reactivity in VS during (nondrug) decision making were less likely to relapse. Activity in a region within the VS, the right putamen, during a Stroop task correlated with verified abstinence from cocaine among a group of treatment-seeking abusers (Brewer, Worhunsky, Carroll, Rounsaville, & Potenza, 2008). In that study, several other regions also correlated with self-reported abstinence including the ventromedial prefrontal cortex (vmPFC), the orbitofrontal cortex (OFC), the superior frontal gyrus/ventral anterior cingulate cortex (ACC), and the posterior cingulate cortex (PCC), but only the putamen also correlated with urine toxicology-verified abstinence. These studies seem to converge in implicating VS reactivity—and particularly its relative reactivity between drug and nondrug stimuli—as a potential indicator of subsequent drug use and relapse.

In the years following the Brewer et al. (2008) study, VS hypoactivity in response to nondrug rewards has emerged as a consistent predictor of relapse and treatment outcome in cocaine dependence. Reduced VS activity during nondrug reward anticipation (Jia, Worhunsky, Carroll, Rounsaville, Stevens, Pearlson, et al., 2011) and reward learning (Stewart, Connolly, May, Tapert, Wittmann, & Paulus, 2014) is linked with lower rates of cocaine abstinence up to a year later. Conversely, increased VS (and insula) reactivity to drug cues predicts greater cocaine use one week later (Prisciandaro, Myrick, Henderson, McRae-Clark, & Brady, 2013). Also, activity during a nondrug working memory task in another subcortical structure, the thalamus, is positively related to treatment effectiveness (Moeller, Steinberg, Schmitz, Ma, Liu, Kjome, et al., 2010). Though there are scattered counter-examples (e.g., increased VS activity to nondrug loss feedback predicted greater relapse among cannabis dependent individuals; Yip, DeVito, Kober,

Worhunsky, Carroll, & Potenza, 2014), the bulk of the emerging evidence implicates drug-cue reactivity and nondrug-cue hypoactivation in subcortical structures, particularly the VS, as a risk factor for relapse and low treatment effectiveness.

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A promising direction for this research is to extend the temporal duration of the prediction beyond the range of two to four weeks reported in most of the studies reviewed here. One way to do that is to start earlier in the lifespan and study addiction risk among youth, before the onset of most addictions. Among adolescents, for example, lower vmPFC activity (and higher superior parietal cortex activity) during response inhibition correlates with greater substance use onset (Norman, Pulido, Squeglia, Spadoni, Paulus, & Tapert, 2011) and greater dependence (Mahmood, Goldenberg, Thayer, Migliorini, Simmons, & Tapert, 2013) in the subsequent 1.5 to 3 years. It is interesting to note that in both of these studies the neural phenotype linked with drug use risk was reduced activity in cognitive control regions (Miller & Cohen, 2001) as opposed to the VS or other subcortical areas that are typically predictive of deleterious outcomes in adults. I will return to the apparent distinction in the predictive ability between cortical and subcortical regions in the following section, but, of course, the story is more nuanced than that simple dichotomy.

Though it is tempting to make an inference based on these results in adolescents, there are also cases where cortical regions are predictive of drug use outcomes in adults. One relatively early study of cocaine dependent adults found that drug cue-induced activity in cortical regions including the precentral gyrus, PCC, and superior temporal gyrus was predictive of worse treatment response across 3 months (Kosten, Scanley, Tucker, Oliveto, Prince, Sinha, et al., 2006). Two other studies targeted error monitoring in the ACC as a candidate process that might

contain predictive information about relapse. Greater error-related negativity (indexed with EEG) during a cocaine-related Stroop task in the first week of treatment was positively related to the number of days of cocaine use at a 3-month follow-up, even when controlling for years of use, craving, and mode of administration (Marhe, van de Wetering, & Franken, 2013).

Activation in the dorsal ACC during the same task was also predictive of relapse when controlling for other factors (Marhe, Luijten, van de Wetering, Smits, & Franken, 2013), further supporting the localization of the error-related negativity to this region (van Veen & Carter, 2002). Thus, the general pattern in terms of predicting illicit drug use is that subcortical structures such as the VS and insula are predictive of lapse and relapse in adults, and prefrontal structures are predictive in adolescents, though there are several exceptions.

Alcohol intake

A small but growing number of studies have deployed the brain-as-predictor approach to study alcohol use and dependence. There are, of course, slight differences in the results between these studies and the ones reviewed above involving nicotine and other drugs, but the similarities are striking and perhaps revealing. In terms of subcortical regions, greater activation in the VS and thalamus to nondrug positive (vs. neutral) affective stimuli is predictive of less alcohol intake and fewer drinking days across 6 months among detoxified alcoholics (Heinz, Wrase, Kahnt, Beck, Bromand, Grusser, et al., 2007). Conversely, greater activation in the VS and insula in response to alcohol (vs. neutral) cues is predictive of accelerating alcohol intake among moderate to heavy drinking adults (Dager, Anderson, Rosen, Khadka, Sawyer, Jiantonio-Kelly, et al., 2014). In terms of cortical regions in adolescents, reduced activation in the middle frontal gyrus and inferior parietal lobule during inhibitory control at baseline predicted a greater risk of heavy drinking up to 3 years later (Wetherill, Squeglia, Yang, & Tapert, 2013). These results are

broadly consistent with the findings for nicotine and other drugs reviewed above in terms of reduced cortical and subcortical activity to nondrug stimuli, and increased subcortical activity to drug stimuli, as predictive of onset and relapse.

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Of course, the narrative never remains so straightforward in the face of growing evidence. In a five-year longitudinal study, greater activity in the middle frontal gyrus, medial temporal lobe, and the preSMA during inhibitory control was *positively* associated with heavy and blackout drinking (Wetherill, Castro, Squeglia, & Tapert, 2013). These findings appear contradictory with the previous result from the same group (Wetherill et al., 2013b), but there may be a few ways to reconcile them. First, the task performance of the (future) heavy drinking participants was indiscriminable from that of the (future) abstinent participants, suggesting that the risky group needed to recruit greater effort to compensate for what otherwise would have been reduced performance and neural activity (Suskauer, Simmonds, Caffo, Denckla, Pekar, & Mostofsky, 2008). Thus, perhaps the risk-prone participants in the previous study were insufficiently motivated for some unknown reason. Second, there may be one or more factors that moderate the predictive effect of prefrontal activity on eventual alcohol use. For example, stress is a reasonable candidate given its known effects on both prefrontal activity and on alcohol use (Sinha, 2001). A recent study supports this possibility by revealing an interaction between VS reactivity and stress on subsequent problem drinking (Nikolova & Hariri, 2012). At low levels of stress, high nondrug reward activity in VS predicted less drinking, but that pattern was reversed at high levels of stress. (The pattern also interacted with amygdala reactivity to threat.) These last few studies hint at the nuance and complexity that will surely emerge as the literature continues to develop over the next few years.

Food intake

An emerging view, propelled in part by strong evidence from neuroscience (Gearhardt, Boswell, & Potenza, 2014), is that food addiction and some kinds of obesity can be conceptualized under the same theoretical framework as addiction to the other substances discussed here (Volkow, Wang, Fowler, & Telang, 2008). Specifically, both drug abuse and certain types of obesity are characterized by disruptions of the reward processing system whereby, through a learning process, the abused substance (drugs or energy-dense foods) comes to dominate the dopamine reward signal at the expense of other stimuli (i.e., nondrug or non-food stimuli). This theoretical framework also assumes that the ability to regulate or control the reward signal through top-down cognitive becomes impaired during addiction. It is from this perspective—and in support of it—that I conclude this section of empirical evidence for the utility of the brain-as-predictor approach for addiction by reviewing pertinent studies on obesity and food addiction.

In a remarkable demonstration of the reward-learning model of food addiction, Burger and Stice (2014) recently showed that a steep (vs. shallow) slope of VS activity during food-cue reward learning was predictive of body mass index (BMI) increases across two years. This basic effect had been established in animals (e.g., Johnson & Kenny, 2010), but to my knowledge this paper represents the first evidence linking food-related reward learning processes to prospective weight gain in humans. Other studies support the more basic hypothesis that dysregulated or hyperactive reward responsibility to palatable food cues is predictive of subsequent eating and weight gain. Among college freshman, increased activity in the VS during passive viewing of appetitive, energy-dense foods predicted subsequent six-month weight gain (Demos, Heatherton, & Kelley, 2012). And activity in the OFC—a cortical region that is part of the dopaminergic

reward pathway and highly interconnected with the VS (Haber & Knutson, 2010)—while viewing appetitive foods was predictive of BMI increase from baseline to one-year follow-up (Yokum, Ng, & Stice, 2011). Together, these studies are broadly consistent with the prediction of the “incentive-sensitization” theory of addiction (Robinson & Berridge, 1993), as applied to food intake, that food addiction is characterized by progressive hypersensitivity to food-related rewards.

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A separate line of research growing out of the emotion regulation tradition (Gross & Thompson, 2009) tests whether craving for appetitive foods can be down-regulated with cognitive reappraisal, and whether the functioning of the neural systems deployed during that kind of self-regulation (summarized in Ochsner & Gross, 2008) are protective against weight gain and/or food addiction. We (Giuliani, Mann, Tomiyama, & Berkman, 2014) and others (Hollmann, Hellrung, Pleger, Schlogl, Kabisch, Stumvoll, et al., 2012; Kober, Mende-Siedlecki, Kross, Weber, Mischel, Hart, et al., 2010; Siep, Roefs, Roebroek, Havermans, Bonte, & Jansen, 2012) showed that reappraisal is effective in reducing food craving and that it recruits a network of brain regions including the dorsolateral PFC, the IFG, and the dorsal ACC that is highly similar to the one involved in reappraisal of other affective states. Furthermore, in our study we found that regulation-related activity in the dorsolateral PFC and several other cognitive control regions related negatively to subsequent change in BMI (Giuliani et al., 2014). Conceptually replicating these findings, incidental activation among fasting participants during food cue viewing in a region commonly implicated in emotion regulation, the dorsolateral PFC (Cohen, Berkman, & Lieberman, 2013), was predictive of food intake immediately after the scan (Cornier, Salzberg, Endly, Bessesen, & Tregellas, 2010). Though the theory and available

evidence supporting the predictive validity self-regulatory processes is relatively new, I view this initial work as an encouraging sign that targeting cognitive control and its associated neural systems is a promising direction for neural prediction of obesity, eating, and potentially other forms of addiction.

From studies that have measured both systems—one related to bottom-up reward reactivity and the other related to top-down self-regulation—there is now some initial evidence that food-related outcomes are the result of a dynamic interaction between of the two. For example, food cue reactivity at baseline in the OFC predicts subsequent snacking (similar to the pattern observed in Yokum et al., 2011), but only among individuals with low self-control as indicated by a questionnaire measure (Lawrence, Hinton, Parkinson, & Lawrence, 2012). Also, in a sample of obese women (who have increased VS responsivity to food cues compared to lean women; Rothmund, Preuschof, Bohner, Bauknecht, Klingebiel, Flor, et al., 2007), reduced activation during a delay discounting task across a large swath of the lateral PFC including the rIFG predicted greater weight gain up to three years later (Kishinevsky, Cox, Murdaugh, Stoeckel, Cook III, & Weller, 2012). As with the research on top-down control reviewed above, this area of research has been highly fruitful despite its relatively young age. Work in these areas have been strongly influenced by dual-process models of impulsivity and control borrowed from psychology and cognitive neuroscience (Chaiken & Trope, 1999; Heatherton & Wagner, 2011), and I expect will continue to expand as new and better models of how multiple processes interact are developed in those disciplines (e.g., Rangel & Hare, 2010). I return to this issue below.

Conceptual considerations in using neuroimaging for predicting addiction outcomes

Several themes emerged during the foregoing review that deserve further elaboration. In the following sections, I briefly describe three of these as they relate to the potential for using

neuroimaging as a predictor of addiction-related outcomes, and discuss how each could be leveraged to gain better traction on the problem at hand. In doing so, I deliberately gloss over some details that may eventually turn out to be important because too few studies exist to make firm conclusions about any particular point beyond the general utility of the brain-as-predictor approach for addiction. Against that backdrop, the following sections are intended to be taken as broad abstractions about aspects of the prediction approach that appear to be important based on the literature so far. As such, I hope that they may influence but by no means constrain future work in this area.

Prediction using cortical versus subcortical brain systems

The first thread that is woven prominently through the studies reviewed here is the separation between cortical and subcortical regions. Why do in some cases cortical and in other cases subcortical regions predict addiction outcomes? The cortical regions that emerged most often are the dorsolateral PFC, the dorsal ACC, and several parietal regions, and the common subcortical regions are the VS and the insula. It is tempting to leap to conclusions about the meaning of these in terms of mental processes (e.g., cognitive vs. affective, controlled vs. automatic, etc.), but there are several alternative possibilities that must first be considered. One is simply that the specific regions that are activated (and are subsequently predictive of addiction outcomes) are in large part driven by the task performed at baseline, and that other regions might have been activated (and predictive) if the investigators had chosen a different task. This problem is further compounded by the fact that the now-dominant models of addiction focus almost exclusively on a competition between reward/impulsivity and self-regulation, so it is logical that the first generation of studies using neuroimaging to predict addiction-related outcomes would focus on tasks that invoke these two processes (and their associated neural

systems) to the exclusion of others. A more complete mapping, as it were, of which brain regions predict which addiction outcomes will require a broader survey of both hypothesized processes and neural instantiations of those processes.

A second problem with ascribing mental process-level interpretations to the subcortical-cortical distinction is the risk of reverse inference error (Poldrack, 2006). As noted above, the general problem with reverse inference (i.e., attributing a specific mental process to an observed neural activation) is that the mapping between the mental and neural levels of analysis is many-to-many. Recent data has shown this to be the case in the area of reward and control specifically. For example, reward value is reflected in part by activity in the dorsolateral PFC (Hare, Malamud, & Rangel, 2011), and cognitive control often recruits regions of the basal ganglia and even the midbrain (Aron, Durston, Eagle, Logan, Stinear, & Stuphorn, 2007; Boehler, Bunzeck, Krebs, Noesselt, Schoenfeld, Heinze, et al., 2011). Just as with the traditional brain-mapping approach in cognitive neuroscience, it is difficult to cleanly ascribe meaning in terms of mental function to a given result when predicting addiction outcomes with neuroimaging data. In fact, there is an explicit tradeoff inherent in the approach between specificity of mental process and prediction accuracy (Berkman & Falk, 2013)—adding more orthogonal regions is likely to increase prediction accuracy, but at the expense of multiplying the number of potential psychological processes that explain why that pattern of activation is predictive.

A third possibility is more statistical but still deserves mention here. Activation in a brain region must have sufficient variability across individuals at baseline to correlate significantly with another measure. (This is true, of course, for both prospective and cross-sectional correlations.) Practically speaking, this means that regions whose activity is homogeneous across participants (e.g., equally high for everyone) are the least likely to be sensitive to individual

differences in outcomes at a later date. This fact may account for some of the surprising findings in the sense that the most task-sensitive regions were at ceiling for many subjects and therefore had limited variance (e.g., incidental activation of cognitive control regions during passive food stimulus viewing; Cornier et al., 2010). This possibility leads directly to a recommendation for neural prediction studies that actually extends to any study of individual difference correlates of neuroimaging data: maximize the meaningful variability across subjects in the predictor task.

Reactivity, regulation, and beyond

I alluded above to the fact that the dominant theoretical models in each of the addiction areas reviewed here focus on (bottom-up) cue reactivity and (top-down) cognitive control as central processes, almost to the exclusion of other potential mechanisms and pathways. This has advantages and disadvantages, of course, and I will begin by discussing the former. The chief upside is that it allows scientists in the field to easily compare results across studies and, in this case, even across addictive substances. The narrow focus of the nicotine, drug use, alcohol, and food intake literatures on reward responsivity allowed for the striking convergence to emerge that VS hypoactivity to nondrug cues was predictive of subsequent behavior across all the substances reviewed here. Another advantage, and perhaps the central motivating one for researchers using neuroimaging in humans, is that the psychological processes associated with craving/urges and self-regulation in humans, on the one hand, and the neural processes associated with wanting/liking and contingency learning in animals, on the other hand, are fairly well characterized. That is to say, if human neuroscience wishes to be placed along a continuum between basic, systems-level research in animals and applied, behavior-level research in humans, then it is prudent to take the early steps into a new research area by following a trail that has been blazed by the neighboring research disciplines. Finally, recent evidence has borne out the

assumption that simple laboratory tasks used to model reactivity and regulation in fact relate in meaningful ways to addiction processes in vivo as measured by ecological momentary assessment (EMA) (Berkman et al., 2011; Wilson et al., 2014b). Altogether, then, emphasizing reactivity and regulation at this early stage in the neural predictors of addiction literature is a reasonable place to begin.

The main drawback of emphasizing the roles of reactivity and regulation is that it may artificially narrow the field's search for additional predictive or otherwise important processes. The strict duality between reactivity and regulation has recently been challenged by other theories that place a single, unified valuation process at the heart of self-regulation (e.g., Inzlicht, Berkman, & Elkins-Brown, in press; Kable & Glimcher, 2007; Rangel & Hare, 2010). In these models, the decision, for example, to smoke a cigarette or have a drink is not the result of a battle between "hot" impulses and "cold" control but rather the output of a valuation calculation and comparison among the possible response options; the valuation process receives inputs from an arbitrary number of sources—some "hot", some "cold", some neither—and enacts the option with the highest subjective value in that moment. A common valuation presents a realistic alternative to the currently dominant dual-process theories and, important for present purposes, suggests that alternative or neural regions be included in prediction models. Specifically, the vmPFC appears to be the locus of a common value integration (Chib, Rangel, Shimojo, & O'Doherty, 2009). This fact is particularly interesting given that this region appeared, unexpectedly, in several places in this review (e.g., Brewer et al., 2008; Norman et al., 2011). The vmPFC is also thought to play an important role during intertemporal choice (Peters & Büchel, 2011), a process that is strongly altered by and perhaps predictive of addiction-related

processes. At the very least, the alternative value integration model warrants further investigation by addiction researchers.

Still, despite its disadvantages, framing the problem in terms of reactivity versus regulation has been highly generative in addiction research, as it has been in other areas (e.g., emotion and self-control; Gross, 1998; Metcalf & Mischel, 1999). Just as it is too early to declare that researchers should begin to look beyond reactivity and regulation, the possibility that these two processes alone can provide a realistic model of addiction cannot yet be abandoned. Rather than embracing either of these two perspectives, then, my goal here is to immunize this young field against the disease of theoretical narrowness that has stultified so many of its kin. Yes, we know a great deal about drug cue reactivity and self-regulation of that reactivity, which can promote research that deepens our knowledge on the role of those processes in addiction; but we also know that addiction is a complex phenomenon that is multiply determined, a full accounting of which will require an a breadth of knowledge that we are nowhere near to attaining. Fortunately, the field is populated by a sufficient number of talented researchers to pursue simultaneously both breadth and depth.

Pediatric versus adult populations

A final issue that surfaced several times in the present review is that the brain systems that were predictive of addiction outcomes in adults were not always the same as those that were predictive in children and adolescents. For example, adult drinking was indexed in several studies by VS hypo/hyperactivity, whereas adolescent drinking was predicted by prefrontal activity (Wetherill et al., 2013a). Setting aside the explanations that the adolescent studies generally used different tasks and were conducted by different research groups than the adult studies, it is a useful exercise to consider some substantive differences between adolescents and

adults that might explain the divergent pattern of results. Most notably, the developmental trajectory of brain growth varies across regions, with subcortical structures maturing relatively early and prefrontal areas lagging behind during adolescence (Casey, Jones, & Hare, 2008; but see Pfeifer & Allen, 2012 for an alternative view that is garnering support from the newest neuroscientific data). Thus, it may be the case that risk for addiction in adolescence is best predicted by individual variability in the development of control-linked prefrontal regions; children whose PFCs are relatively well developed and functioning at baseline are less likely to engage subsequently in risky behaviors. This interpretation fits with the broad pattern that greater PFC activity at baseline during adolescence is a protective factor against alcohol and drug use (Norman et al., 2011; Wetherill et al., 2013a). Another possibility is that the shifting social landscape during adolescence promotes risk in peer contexts to the extent that youth are vulnerable to peer influence (Steinberg & Monahan, 2007), so adolescents who are able to recruit self-regulatory resources generally, and in those contexts specifically, would be less likely to use substances. Of course, these two possibilities are not mutually exclusive, and in any case adolescence presents a highly promising time to use neuroscience methods both to assess for substance-use risk and to develop neurally-informed interventions to reduce that risk (Berkman, Graham, & Fisher, 2012). It is early yet, but the data on prediction during adolescence is unambiguous on the point that this is a complex time characterized by rapid neural and social changes. As a cautionary note, the extraordinary potential of research in this area to produce insights about addiction is weighted against the formidable combination of neuroscience, developmental, and statistical expertise necessary to produce them.

Future directions and conclusions

The rapid acceleration of research using neuroimaging to predict addiction outcomes in the last two to three years presents ample reason to be optimistic about this area of the addiction literature. The studies reviewed here draw upon a diverse range of theories from addiction, social and developmental psychology, and even behavioral economics to provide new and creative ways to study, understand, and, yes, even predict addiction outcomes. The results of the studies support existing ideas in addiction (e.g., the incentive-sensitization hypothesis), present new ways to test those ideas, and provide insights and information that would otherwise be unavailable. My prediction about the future of the neural prediction literature is sanguine.

As good as things are now, I see three areas where prediction research could grow even further in the future. First, a key limitation inherent in the approach is the sacrifice of process-level specificity for prediction accuracy. Adding more orthogonal brain regions or tasks at baseline will necessarily increase prediction accuracy and simultaneously decrease the ability to attribute the prediction to a specific mental process. Meta-analytic approaches such as the ambitious NeuroSynth project (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011) are explicitly designed to circumvent this problem and will be central to future efforts to map results and/or hypotheses from prediction studies onto psychologically meaningful constructs. Second, it may be taken for granted that the ability of neuroimaging to predict outcomes is limited in part by the quality of the measurement of those outcomes. EMA represents an innovative approach to improve the nuance and reliability of the addiction outcomes, and indeed a handful of studies have begun to combine it with neuroimaging (Wilson et al., 2014b). This synthesis is particularly valuable in light of the fact that EMA can capture processes that are one step closer to those being measured in the neuroimaging laboratory while still maintaining a high degree of ecological validity (e.g., Berkman et al., 2011). As such, the merging of EMA and fMRI

represents a way to bridge a critical gap between very specific, process-level studies in the laboratory (e.g., that isolate inhibitory control) and very broad, outcome-level studies in the real world (e.g., that measure substance use rates across two years). And third, I would be remiss to omit the explosion of prediction research that has occurred in parallel to this one using other imaging modalities, notably connectivity and structure. For example, increased VS volume is associated with greater rates of abstinence from cannabis across three weeks (Yip et al., 2014), and resting state connectivity within the cognitive control predicted cigarette-smoking status (Pariyadath, Stein, & Ross, 2014). A thorough review of such studies is outside the scope of this chapter, but it remains within bounds to suggest that they will be important, alongside studies using functional imaging, for the future of prediction research. Together, this work will build upon the available brain-mapping knowledge of addiction processes to provide tangible information that will directly inform treatment and intervention.

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Table 1. Brain-as-predictor studies of nicotine and tobacco

Study	Substance	Population	Prediction Duration	Task Type	Predictive Region(s)
Berkman et al. (2011)	Nicotine/Tobacco	Adults	3 weeks	Regulation – General Go/No Go Task	rIFG, BG, preSMA
Falk et al. (2011)	Nicotine/Tobacco	Adults	1 month	Reactivity – Specific Cigarette Ads	mPFC
Chua et al. (2011)	Nicotine/Tobacco	Adults	4 months	Reactivity – Specific Message Task	dmPFC
Janes et al. (2010)	Nicotine/Tobacco	Adults	1 day	Reactivity – Specific Emotional Stroop	Anterior insula
Versace et al. (2011)	Nicotine/Tobacco	Adults	10, 12, 24 weeks	Reactivity – Specific Cigarette Related Images	Posterior visual association areas
Versace et al. (2014)	Nicotine/Tobacco	Adults	6 months	Reactivity – Specific Cigarette-Related Cues	Posterior visual association areas, dorsal striatum, mPFC, dlPFC
Wilson et al. (2014a)	Nicotine/Tobacco	Adults	Directly Following fMRI scan	Reactivity –Specific - Anticipated Cigarette Related Reward	Ventral Striatum

Note. BG = basal ganglia; dlPFC = dorsolateral prefrontal cortex; dmPFC = dorsomedial prefrontal cortex; mPFC = medial prefrontal cortex; preSMA = presupplementary motor area; rIFG = right inferior frontal gyrus.

Table 2. Brain-as-predictor studies of illicit drugs

Study	Substance	Population	Prediction Duration	Task Type	Predictive Region(s)
Paulus et al. (2005)	Methamphetamine	Adults	1 year	Reactivity – General Decision Making Task	Insula, inferior parietal lobe, middle temporal gyrus, cingulate, ventral striatum
Brewer et al. (2008)	Cocaine	Adults	1, 3, 7 days	Regulation – General Color Stroop Test	VS, right putamen, vmPFC, OFC, superior frontal gyrus/ACC, PCC
Jia et al. (2011)	Cocaine	Adults	8 weeks	Reactivity – General Monetary Incentive Delay Task	VS, medial frontal gyrus, thalamus, right subcallosal gyrus, insula, left amygdala
Stewart et al. (2014)	Cocaine	Adults	1 year	Reactivity – General Reward Learning Task	VS, bIFG, anterior insula
Prisciandaro et al. (2013)	Cocaine	Adults	1 week	Reactivity – Specific Drug Cues; Regulation – General Go/No Go Task	VS, insula
Moeller et al. (2010)	Cocaine	Adults	16 weeks	Reactivity – General Working Memory Task	Thalamus
Yip et al. (2014)	Cannabis	Adults	3 weeks	Reactivity – General Nondrug Loss Reactivity	VS
Mahmood et al. (2013)	Eight illicit drugs, alcohol, marijuana, and nicotine	Adolescents	18 months	Regulation – General Go/No Go Task	vmPFC, superior parietal cortex
Kosten et al. (2006)	Cocaine	Adults	3 months	Reactivity – Specific Drug Cues	Precentral gyrus, PCC, superior temporal gyrus

Marhe et al. (2013a)	Cocaine	Adults	3 months	Regulation – Specific Drug Stroop Task	ACC
Marhe et al. (2013b)	Cocaine	Adults	3 months	Regulation – General Eriksen Flanker Task	Dorsal ACC

Note. ACC = anterior cingulate cortex; bIFG = bilateral inferior frontal gyrus; OFC = orbitofrontal cortex; PCC = posterior cingulate cortex; vmPFC = ventromedial prefrontal cortex; VS = ventral striatum.

Table 3. Brain-as-predictor studies of alcohol

Study	Substance	Population	Prediction Duration	Task Type	Predictive Region(s)
Heinz et al. (2007)	Alcohol	Adults	6 months	Reactivity – General Positive Stimuli Cues	VS, thalamus
Dager et al. (2014)	Alcohol	Adults	1 year	Reactivity – Specific Alcohol Image Cues	VS, insula
Wetherill et al. (2013a)	Alcohol	Adolescents	5 years	Regulation – General Go/No Go Task	Middle frontal gyrus, inferior parietal lobe, preSMA
Wetherill et al. (2013b)	Alcohol	Adolescents	3 years	Regulation – General Go/No Go Task	Middle frontal gyrus, medial temporal lobule
Nikolova et al. (2012)	Alcohol	Young Adults	3 months	Reactivity – Unknown* Reward Responsiveness	VS, amygdala

Note. preSMA = presupplementary motor area; VS = ventral striatum.

*No data on whether the reward stimulus presented was general or alcohol specific

Table 4. Brain-as-predictor studies of food intake and obesity

Study	Substance	Population	Prediction Duration	Task Type	Predictive Region(s)
Burger et al. (2014)	Food	Adolescents	2 years	Reactivity – Specific Cue-Reward Learning	VS
Demos et al. (2012)	Food	College Freshmen	6 months	Reactivity – Specific Food Image Viewing	VS
Yokum et al. (2011)	Food	Adolescents	1 year	Reactivity – Specific Food Image Viewing	OFC
Lawrence et al. (2012)	Food	Adult	1 hour	Reactivity – Specific Food Image Viewing	OFC
Kishinevsky et al. (2012)	Food	Adult	3 years	Regulation – General Delayed Discounting Task	VS, lateral PFC (rIFG)

Note. OFC = orbitofrontal cortex; PFC = prefrontal cortex; rIFG = right inferior frontal gyrus; VS = ventral striatum.