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# Neural Recruitment During Self-Control Of Smoking: A Pilot fMRI Study

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# What Is Addiction?

edited by Don Ross, Harold Kincaid,  
David Spurrett, and Peter Collins



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## 10 Neural Recruitment during Self-Control of Smoking: A Pilot fMRI Study

John R. Monterosso, Traci Mann, Andrew Ward, George Ainslie, Jennifer Bramen, Arthur Brody, and Edythe D. London

This chapter presents pilot data from a neuroimaging study that recorded changes in functional magnetic resonance (fMRI) signal (an indirect indication of changes in brain activity) while overnight abstinent cigarette smokers were given opportunities to smoke, but were asked to try to resist the temptation to do so. This is the first study of which we are aware that has used fMRI to identify substrates of self-control of an addictive behavior.

### Inhibitory Control in Addiction Research

Until recently, neuroscience research on addiction has focused primarily on mechanisms of reinforcement. In the mid-twentieth century, *negative* reinforcement dominated the field, as relief of withdrawal (including “conditioned withdrawal”) was viewed as the primary underlying basis for pathological drug use (Jelinek 1960). For reasons that included a spike in use of crack cocaine, which is associated with much less obvious withdrawal symptoms than alcohol and opioids, emphasis in the late twentieth century shifted away from negative reinforcement. Withdrawal cannot account for all pathological cocaine use, particularly since conditioned responses to cocaine-related cues generally are more *drug-like* than *drug-opposite* (e.g., tachycardia rather than bradycardia; Carter and Tiffany 1999). Indeed, *positive* affect is a common trigger for relapse to cocaine abuse (Shulman 1989). It became clear that positive reinforcement is central to pathological drug use. Dramatic progress was made in the neuroscience of drug reward during the late twentieth century (Koob 1996; Schultz 1997; Wise and Rompre 1989). Especially important in this regard was the recognition that midbrain dopaminergic neurons that project to the nucleus accumbens participate prominently in mediating reward from all drugs of abuse (Pontieri et al. 1996).

Still, negative and positive reinforcement alone do not fully describe the territory that the science of addiction must address. Consider the smoker who wants to quit. This person might utilize a pharmacological aid that reduces withdrawal from smoking cessation (e.g., nicotine replacement therapy) or that reduces the positive reinforcement

from smoking (e.g., varenicline, a partial agonist for nicotinic receptors, that, among other effects, reduces the reward from smoking). But in addition, this person also *tries* to quit. What does it mean to try to quit drug use, that is, to try not to continue using? This aspect of addiction is, we think, central to everyday thinking about the topic. It is this aspect of the phenomenon that the eminent psychologist Frank Logan had in mind when he wrote, “Principles of animal behavior can provide a basis for a theory of human drug use and abuse, but voluntary control of addictive behavior requires uniquely human cognitive processes” (Logan 1993, 291).

In the last decade, addiction researchers have paid more attention to understanding the basis of “voluntary control of addictive behaviors” and its failing (Goldstein and Volkow 2002; Jentsch and Taylor 1999; London et al. 2000). Grant (2004) described this as the beginning of a third and as yet unproven wave of addiction research (negative and positive reinforcement being the first two). The research on voluntary control has proceeded in parallel along several lines, variously labeled as investigations of *inhibitory control*, *executive function*, *impulse control*, *cognitive control*, *self-control*, *self-regulation*, and *willpower*. This chapter uses Logan’s descriptive phrase “voluntary control of addictive behaviors” throughout, and does not attempt to interrelate the various processes or subcategories of the constructs named above. We will, however, describe three approaches to the area of research in order to provide the context for the study presented here. We say from the outset that we do not think it inevitable, or even likely, that all cognitive processes that underlie voluntary control of addictive behaviors will be able to be mapped onto identifiable neurobiology (see Ross 2005). However, even in the absence of complete reductionism, there may well be an opportunity to illuminate neural substrates relevant to the voluntary control of addictive behaviors.

### **Good Decision Making and the Voluntary Control of Addictive Behavior**

Abstinence from drugs of abuse is a *rational* (i.e., utility-maximizing) choice given anticipated negative consequences of continued drug taking. Individual differences in the capacity for rational decision making may therefore constitute a substantial determinant of problem drug use. Laboratory tasks have been constructed to isolate aspects of decision making that are thought to be relevant to drug use (Bechara and Damasio 2002; Bechara, Dolan, and Hinds, 2002; Kirby, Petry, and Bickel 1999; Rogers et al. 1999). Typically, these tasks require individuals to select repeatedly from sets of alternatives designed to isolate one or more factors, such as *risk*, *uncertainty*, or *delay*. The most common approach has been to compare the performance of drug abusing and nonabusing participants on such tasks, and in some cases, to pair the tasks with neuroimaging. This research asks, “What decision-making factors differ between drug abusers and comparison subjects who do not abuse drugs?” and, in some cases, “How do

drug abusers and comparison subjects differ in neural activity associated with decision making?"

Although generalizing is complicated by the myriad factors that differ from one study to another, including the history and severity of drug dependence, the duration of abstinence prior to assessment, and specifics of the methodology employed, drug-abusing and non-drug-abusing populations appear to differ with respect to decision making. In particular, drug-abusing subjects appear to be less risk averse (Fishbein et al. 2005; Rogers and Robbins 2001), less sensitive to unpredictable penalties (Bartzokis et al. 2000; Bechara 2001; Fishbein 2000; Grant, Contoreggi, and London 2000; Mazas, Finn, and Steinmetz 2000), more driven by reinforcement history in the most immediate past (Paulus et al. 2002, 2003), more prone to behave in accordance with local versus global reinforcement rates (Heyman and Dunn 2002), and more willing to trade reward value for reward immediacy (Bickel, Odum, and Madden 1999; Cairns and van der Pol 2000; Coffey et al. 2003; Fuchs 1982; Kirby and Petry 2004; Kirby, Petry, and Bickel 1999; Mitchell 1999; Moeller and Dougherty 2002; Petry 2003; Reynolds et al. 2004; Vuchinich and Simpson 1998).

Studies comparing neural activation (inferred through neuroimaging) during performance of decision-making tasks have revealed significant anomalies among drug abusers. Although there is some inconsistency, most studies have reported hypofrontality among drug abusers during decision making, especially within the dorsolateral prefrontal cortex (DLPFC) (Bolla et al. 2003, 2005; Ersche et al. 2005; Paulus et al. 2002, 2003). Of course, cohort studies that compare drug abusers and nonabusers suffer shortcomings including indeterminacy regarding whether group differences predated substance abuse. In an important extension of cohort comparison findings, low recruitment during a two-choice guessing task within a network of regions involved in decision making (including the right middle frontal gyrus, middle temporal gyrus, and posterior cingulate) was associated with subsequent relapse among abstinent methamphetamine abusers (Paulus, Tapert, and Schuckit 2005).

Although repeated reports of decision-making anomalies among drug abusers suggests the importance of decision making to the behavior, decision-making tasks may not capture processes engaged during the struggle between a strong desire to use drugs and conflicting goals such as commitments made to abstain from drug use. Indeed, while small amounts of money have been put at stake in some decision-making tasks, the majority of the research in this area has used hypothetical choices (Madden et al. 1997; Monterosso et al. 2001) or decision-making games where "points" provide the only task incentive (Bechara and Damasio 2002; Rogers et al. 1999). Although a steeper discounting of reward as a function of delay has, for example, been repeatedly shown in drug abusers (Bickel, Odum, and Madden 1999; Cairns and van der Pol 2000; Coffey et al. 2003; Fuchs 1982; Kirby and Petry 2004; Kirby, Petry, and Bickel 1999; Mitchell

1999; Moeller and Dougherty 2002; Petry 2003; Reynolds et al. 2004; Vuchinich and Simpson 1998), the difference appears as a *preference*. An individual who says that she would, hypothetically, choose \$10 today over \$20 in a week may be making a bad decision, possibly even reflecting a tendency that puts her at risk for substance abuse. But (to our knowledge) there is no evidence that the decision entails the type of ambivalence or motivational struggle that is associated with voluntary control of an addicted behavior.

### **Behavioral Inhibition and the Voluntary Control of Addictive Behavior**

An alternative approach to studying the voluntary control of addictive behavior looks at capacity for *behavioral inhibition*. According to this idea, behavioral inhibition, which can be loosely defined as the *intentional suppression of prepotent responses that are goal-inappropriate*, is critical to recovery from addiction, because recovery requires the suppression of rapid, conditioned responses so that slower mechanisms can guide behavior (Fillmore 2003; Jentsch and Taylor 1999). If this conjecture is correct, deficiency in behavioral inhibition could serve as a behavioral phenotype for substance-abuse disorders, facilitating the search for genetic linkages and physiological markers. Established paradigms that tax behavioral inhibition are easily paired with imaging methodologies. Below we consider first the construct of behavioral inhibition, and then the limits of evidence linking it to addiction.

Several behavioral inhibition subtypes have been proposed, with perhaps the most agreed-upon subclassifications being “response inhibition” versus “interference control” (Barkley 1997). *Response inhibition* is the intentional cancellation of a behavior already underway, as when a baseball batter attempts to stop (“check”) his swing at a pitch outside the strike zone, or as when a speaker attempts to cut off an utterance she realizes is inappropriate. *Interference control* refers to protecting ongoing processes from interference so that they *can* be completed, as when a speaker tries to avoid distraction by a neighboring conversation. Although both functions are generally included under the heading of inhibitory control, performance on response inhibition tasks such as the Stop Signal (SST) and go/no-go tasks is not strongly correlated with performance on interference control tasks such as the Color-Word Stroop Task and the Flanker Task (in Friedman and Miyake 2004,  $r = .15$ ; in Avila et al. 2004,  $r = -.11$ ).

The clinical literature has strongly implicated the frontal lobes in both types of behavioral inhibition. Frontal lobe lesions cause dramatic impairment on both response inhibition and interference control tasks (Aron et al. 2003; Perret 1974). There has been a recent spate of studies that have paired behavioral inhibition tasks (especially the Stroop, go/no-go, and SST) with neuroimaging methodologies (Bush et al. 1999; Garavan et al. 2002; Hester and Garavan 2004; Kaufman et al. 2003; Peterson et al. 1999; Rubia et al. 2005). In general, these studies corroborate findings from the clinical



literature, demonstrating an association between performance on inhibitory tasks and activation of the frontal lobes (we will defer discussion of more specific localization for the time being).

Several studies have reported an association between deficits in behavioral inhibition and substance-abusing populations (Fillmore and Rush 2002; Monterosso et al. 2005; Salo et al. 2005). In addition, two studies pairing versions of the go/no-go task with fMRI found less recruitment in the frontal cortex and in the anterior cingulate cortex and presupplementary motor area among cocaine abusers than in control subjects (Hester and Garavan 2004; Kaufman et al. 2003). As with cohort comparisons of decision-making anomalies, it is not possible to determine whether impairment in response inhibition follows drug use (as a consequence) or precedes (perhaps predisposes to) drug abuse.

Although it has been argued that the ability to resist temptation relies on the capacity for behavioral inhibition (Mahone et al. 2002), it is unclear how much behavioral inhibition, as measured by speeded cognitive tasks, captures functioning that is important for maintaining abstinence. Errors on behavioral inhibition tasks result from prepotent responses that are only transiently dominant, and such errors depend on the speeded nature of the tasks. Typically a respondent is aware of committing an error even while completing the response, and would correct it promptly if given the chance. By contrast, even when drugs are readily available, using them requires the execution of an action plan that remains dominant for seconds; and although the user may experience ambivalence, self-correction does not reliably occur at all, let alone within a few hundred milliseconds. In short, although behavioral inhibition *may* be integral to self-control of drug taking, dissimilarities between the phenomena warrant skepticism regarding whether speeded inhibition tasks really correspond to resisting everyday temptation.

### The “Self-Control Challenge”

There is emerging interest in studying the voluntary control of addictive behavior with laboratory tasks that more directly model the real-world phenomenon. For example, Childress and colleagues conducted an imaging protocol in which they assessed what circuitry was recruited when individuals actively attempted to suppress craving for cocaine (Childress et al. 2003, 2004). Following the most well-established technique for eliciting craving in drug abusers during brain image acquisition (Childress et al. 1999; Grant et al. 1996), Childress and colleagues presented video cues depicting drug use to a group of cocaine abusers. Participants were instructed to allow themselves to crave in one condition, and to attempt to stop their craving in another condition. Preliminary reports of that work indicated that relative to the condition in which craving was not suppressed, attempts to inhibit craving recruited robust activation in inferior frontal

gyri (Childress et al. 2003, 2004). A similar design was recently used in a study of cigarette smokers; attempt to suppress the urge to smoke resulted in activation of the dorsal anterior cingulate cortex (dACC) and posterior cingulate cortex (Brody et al. 2007).

Although the suppression of craving may constitute a more direct model of the voluntary control of an addictive behavior than a speeded cognitive task like the Stroop, it is also problematic. Since the relationship between craving and drug abuse is itself not straightforward (Tiffany 1999; Tiffany et al. 1993), it is unclear how much the explicit target of inhibitory control (craving) is relevant in achieving abstinence. For example, empirical evidence suggests that at least in early recovery, the difference between more and less effective treatment is not reflected in the amount of craving reported, but rather in the frequency of drug use given the presence of high craving (Weiss et al. 2003). The recent development of methodologies for delivering primary rewards during fMRI (e.g., McClure, Berns, and Montague 2003) allows for more direct analysis of this phenomenon.

### **Pilot Study of Smoking Self-Control**

We used a specialized MRI-compatible device for delivering cigarette smoke to allow us to study the brain activity associated with the voluntary control of smoking behavior in regular cigarette smokers. The goals were (1) to establish the viability of the method for use in larger studies, and (2) to collect preliminary evidence regarding the brain regions that are active when abstinent cigarette smokers voluntarily abstain from an opportunity to smoke.

### **Method**

Ten smokers, who were not seeking treatment, were recruited from a list of previous research participants who gave permission for further contact. All had been previously screened for the presence of Axis I disorders. At a baseline screening session, participants were given a full explanation of the procedures and provided informed consent in accordance with the University of California Institutional Review Board. They completed a magnetic resonance imaging safety screening form, and were in good general health, right handed, and 18–50 years of age. They reported smoking 10 or more cigarettes per day, and had  $\geq 18$  ppm CO in their expired breath in the screening session. Potential participants were excluded if they reported a history of neurological disease (e.g., stroke) or of head trauma, reported claustrophobia (which would preclude fMRI), or were pregnant.

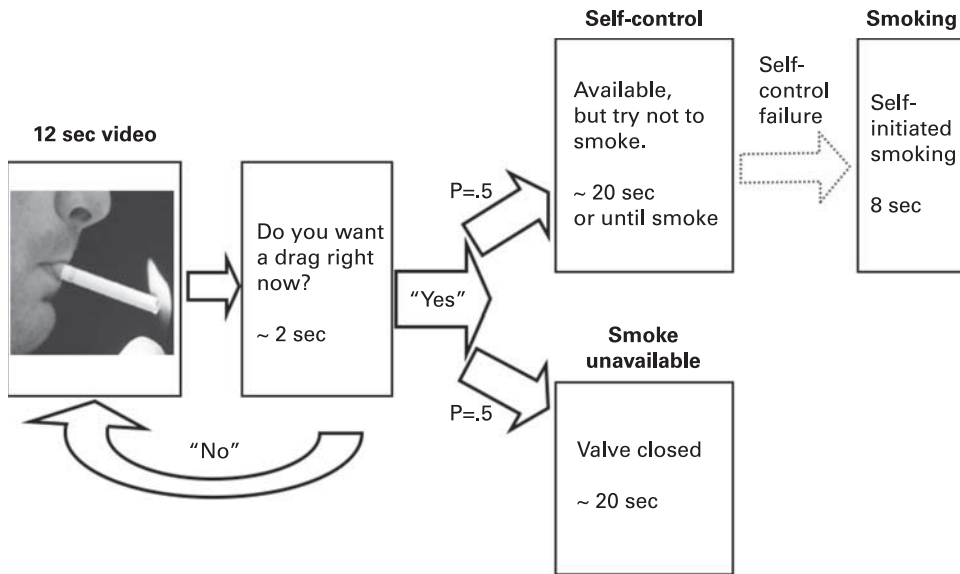
During the baseline test session, the participants were trained to smoke through the “MRI-Hookah,” a specialized smoking device that is compatible with the MR environment. To approximate the scanning environment, participants were positioned supine on a cot, and fit with their own Silastic mask. After smoking through the apparatus,

participants were asked to rate the experience of smoking through the hookah on a scale between  $-10$  and  $+10$  with the following anchors provided:  $-10 =$  “very unpleasant,”  $-5 =$  “moderately unpleasant,”  $0 =$  “neither pleasant or unpleasant,”  $+5 =$  “moderately pleasant,” and  $+10 =$  “very pleasant—equal to normal smoking.” Participants in the baseline session were invited to participate in fMRI testing only if they reported (1) smoking  $> 10$  cigarettes per day, had CO scores  $> 18$  ppm, and rated smoking through the MRI-Hookah as at least a “ $+5$ ” (moderately pleasant). Participants included in the study were predominantly female (6 of 10) and Caucasian (8 of 10). The mean age of participants was  $30.3 \pm 4.5$  and the mean number of cigarettes smoked per day (according to self-report) was  $16.3 \pm 3.2$ .

Subjects were instructed to abstain from smoking for 12 hours before their scheduled participation in the Smoking Self-Control Challenge. CO was assessed at the beginning of the test session to verify abstinence ( $\leq 8$  ppm was required). After completing the Smoking Self-Control Challenge (described below) subjects were again assessed for CO in expired breath. Participants were then asked to indicate how difficult they found it to refrain from smoking on “self-control” test blocks. To increase the desire to smoke during the task, participants were informed that an additional 1.5 h of monitored abstinence would be required after they completed the task.

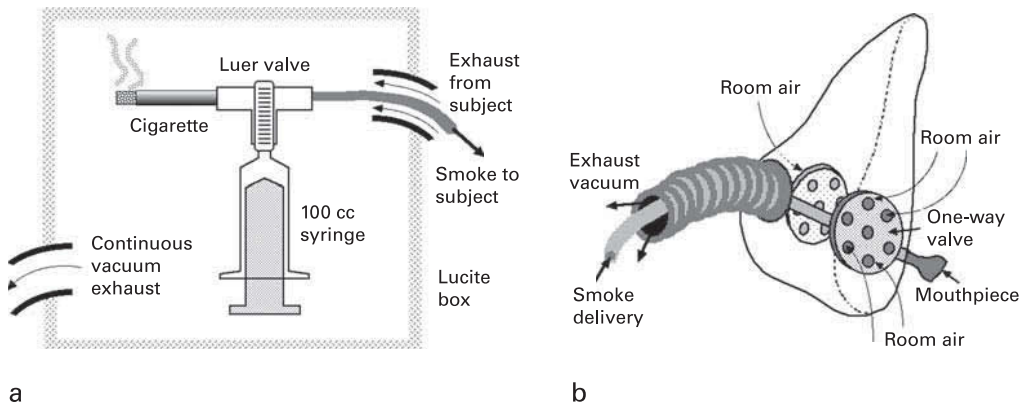
### Self-Control Challenge Task Design

Prior to the Smoking Self-Control Challenge, participants were read task instructions and given a practice of several trials (outside the scanner). Most important, the instructions informed participants that there would be times during the task in which they would have access to cigarette smoke, but during which they should try to refrain; *“We’d really like it if you could try not to smoke on as many of these rounds as you can manage. . . . We realize that it may be difficult to resist smoking, but try your best.”* Our goal in choosing this particular wording was both to encourage self-control efforts, but at the same time, to convey that failure was not tantamount to breaking the rules of the experiment. Figure 10.1 provides a schematic of a single trial of the Smoking Self-Control Challenge. Each trial began with a 12-second video clip of smoking cues (e.g., a cigarette being lit). After the clip, subjects were asked to indicate whether or not they wished to smoke (see below). If they responded in the affirmative, depending on the particular trial, subjects were either informed by the computer (1) “Smoke available—but try not to,” or (2) “Valve closed, smoke unavailable”). An experimenter outside the scanner room signaled to an assistant inside the scanner room which type of trial was about to begin, and the assistant positioned the valve accordingly. During self-control trials, the assistant inside the scanner room watched the cigarette that was held in tubing within the MRI-Hookah (see figure 10.2). Inhalation on the part of the participant was readily detected as a brightening of the ambers at the end of the cigarette. The



**Figure 10.1**

Schematic of one trial of the Self-Control Challenge. Each of two task runs consisted of twelve trials.



**Figures 10.2**

MRI-Hookah. A. Schematic representation of the fully enclosed continuously vented smoking apparatus. B. Facemask used by the subject to inhale smoke. The smoke is delivered through the center cannula of a concentric dual hose apparatus. The expired smoke is exhausted through the outer tube.

occurrence of inhalation was signaled to the experimenter, who recorded the event through a button press on the computer that ran the experimental task. During these trials, if subjects smoked, the computer presented the word “Smoking” to the participant for 5 sec. On “Smoke Unavailable” trials, the aforementioned “Valve closed, smoke unavailable” message appeared on the screen for the trial duration. Each task run was conducted until 6 Smoke-Unavailable and 6 Self-Control trials were completed (regardless of how many times the participant abstained on those trials). Each participant completed two task runs lasting approximately 8 minutes, separated by a short break. After completing each imaging session, participants were asked to rate how difficult they found it to *not smoke* on self-control trials.

### The MRI-Hookah

The MRI-Hookah was developed to allow cigarette-smoke inhalation simultaneous to image acquisition (R21 DA13627-02; *Enabling Technologies in fMRI and Cigarette Smoking*, PI Cohen). The device introduces no MRI artifacts, allows the subject to inhale and exhale both smoke and room air through nose or mouth, and quickly removes smoke and excess odors so that these secondary reinforcers may be kept under experimental control. It delivers smoke to the subject through a close-fitting Silastic mask, which includes a mouthpiece that the subject places comfortably in his or her teeth (figure 10.2a and 10.2b).

Use of a standard surgical oxygen mask ensured that the subjects are able to breathe through both the nose and mouth. Air was expired through a low-velocity vacuum system, which draws air continuously through a large-bore tube, fitted concentrically around the smoke delivery tube. When cigarette smoke was made available, a gated valve within the MRI-Hookah was opened, allowing smoke to be drawn through the mouthpiece. When the subject was not inhaling cigarette smoke, one-way valve ports on the side of the mask passed room air freely. In this way the smoke odor, which might act as a secondary reinforcer and therefore a contaminant in experiments, was removed from the environment as quickly as possible.

### MRI Data Acquisition

**Imaging parameters** We used a 3-Tesla Siemens Allegra system for all acquisitions (see note for details<sup>1</sup>). Stimuli were displayed on magnet-compatible video goggles (Resonance Technology, Northridge, CA). This display presents VGA screen resolution (800 × 600 pixels with 24-bit color depth) with a nominal visual angle of about 30° horizontally and 20° vertically. Correction for individual myopia or hyperopia was accomplished by the insertion of lenses. During the scans, subjects responded to the “yes/no” question regarding whether they wanted to smoke by pressing a two-button magnet-compatible keypad. The touch pad was placed under the fingers of the subject’s dominant hand (right only, per inclusion criteria).

## Image Analysis

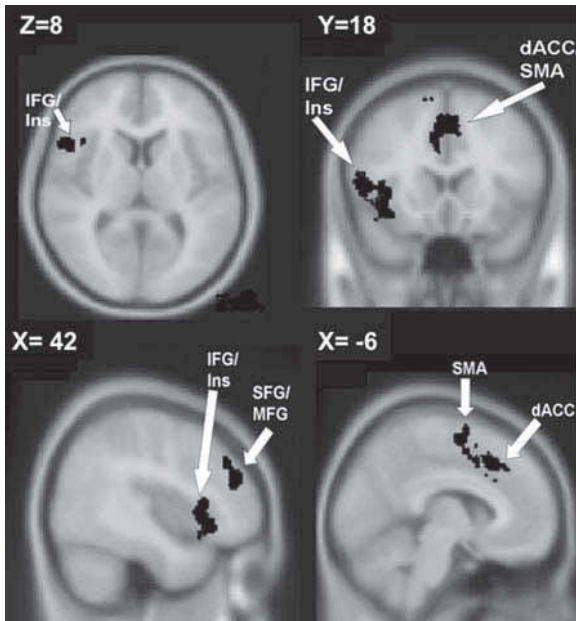
**Functional image processing and analysis** Preprocessing procedures are described in the note below.<sup>2</sup> Subsequent to preprocessing, both task runs for each subject were analyzed individually in the first level of analysis. For each participant, a second-level analysis combined the Z-statistical maps from the task runs (except for one participant, for whom one run was discarded due to excessive head motion). The resulting statistical maps from these second-level analyses (also Z-statistic maps) served as inputs for group analyses (“third level”). Activation maps for main effect consist of voxels with  $Z > 2.3$ , with cluster-level significance (correcting for whole brain search) of  $p < .05$ .

## Results of Smoking Self-Control Challenge Pilot Study

Subjects voluntarily abstained on 56.2% of Self-Control trials. No subject smoked on all Self-Control trials, and only one subject abstained on all Self-Control trials. Subsequent to the experiment, the participants reported a mean rating of difficulty in maintaining self-control of  $6.9 \pm 2.1$  (of a possible 10). For the primary contrast, we assessed the difference between fMRI signal during Self-Control trials in which the participant succeeded (Voluntary Abstinence) and Smoke-Unavailable trials. Self-Control trials in which the participant smoked were excluded from this contrast, in part because of artifacts related to smoking.

The primary imaging results are presented in figure 10.3 (*in radiological space*). Three clusters were identified in which the fMRI signal was greater during Voluntary Abstinence trials, relative to Smoke Unavailable trials. The largest cluster (1,769 voxels; fig. 10.3, top right and bottom right) included portions of the dorsal anterior cingulate cortex (dACC, BA32) and supplementary motor area (SMA BA8 and BA6). A second cluster of significant extent (654 voxels; fig. 10.3, bottom left) was observed in the right superior and middle frontal gyri (SFG, MFG, BA9; encompassing more medial aspects of the DLPFC). A third cluster of significant extent (577 voxels; fig. 10.3, top left, top right, and bottom left) was centered in the right inferior frontal gyrus and encompassed part of the insula as well (IFG, BA 47, extending to BA 45).

Deactivations in the primary contrast (i.e., clusters in which BOLD signal was greater during Smoke-Unavailable than Voluntary Abstinence trials) were also identified (though are not presented visually). The largest cluster of deactivation (1,532 voxels) was observed in the posterior cingulate cortex (PCC) and extended dorsally into the precuneus (BA 30 and 31). The next largest cluster (895 voxels) was observed in the ventral portion of the medial frontal gyrus and in the orbital gyrus (BA 11). The third cluster of deactivation (711 voxels in extent) was observed in the dorsomedial frontal gyrus and paracentral lobule (BA 6 and 5). The smallest cluster of deactivation (605 voxels in extent) was centered on the border between the angular gyrus and postcen-



**Figure 10.3**

Results from whole brain results in radiologic space for Voluntary Abstinence—Smoke Unavailable with significant activations in black (voxel  $z > 2.3$ , maximum  $z = 3.7$ , cluster level corrected significance of  $p < .05$ ). Increases in BOLD signal during Voluntary Abstinence were observed in a large cluster encompassing portions of the dACC and SMA, and smaller clusters in the right DLPFC (SFG/MFG) and the right VLPFC (IFG), which encompassed part of the insula as well.

tral gyrus, encompassing portions of each within the right hemisphere (BA 2, 3, and 40).

### Discussion

Our primary goal was to develop a methodology for examining the neural activity during voluntary control of smoking behavior. In order to accomplish this, we developed a method for making cigarette smoke available in the scanner (*R21 DA13627-02; Enabling Technologies in fMRI and Cigarette Smoking*, PI Cohen). Smokers were then faced with a situation in which the opportunity to smoke was available, though discouraged, on some trials, whereas it was unavailable on other trials. It was necessary that the procedure be sufficiently comfortable for participants that the relevant opportunity to smoke remained attractive. The fact that participants' self-reports indicated that they found it difficult to not smoke on the trials in which smoke was available (6.9 on a 10-point scale) indicates that this objective was met.

Although both sides of the contrast included no physical behavior, relative to trials in which smoke was not available, voluntary abstinence recruited activity in a network of regions predominantly within the prefrontal cortex. In characterizing their influential integrative theory of prefrontal cortical functioning, Miller and Cohen (2001, 171) write: "We assume that the PFC serves a specific function in cognitive control: the active maintenance of patterns of activity that represent goals and the means to achieve them. They provide bias signals throughout much of the rest of the brain, affecting not only visual processes but also other sensory modalities, as well as systems responsible for response execution, memory retrieval, emotional evaluation, etc." At a very general level, the activation of lateral portions of the prefrontal cortex may have served the top-down biasing of the action plan to *not smoke*. The network of regions "deactivated" (i.e., those regions that showed relatively diminished activity during the Voluntary Abstinence trials) in the primary contrast (including the ventromedial prefrontal cortex and posterior cingulate cortex) are consistent with the "resting network"/"default network" identified during fMRI (i.e., the set of brain regions observed to consistently deactivate during active task states; Buckner and Vincent 2007). This provides further indication that not smoking when smoke was available was associated with more cognitive processing than was not smoking when cigarette smoke was not available.

Although current knowledge of the functional specificity of the aforementioned brain regions is insufficient to permit conclusive "reverse inferences" from region to underlying function, we can offer some further speculation. The observed network is consistent with the functional characterization of voluntary abstinence as including top-down maintenance of task goals in working memory (prominently linked to the dorsolateral prefrontal cortex; Levy and Goldman-Rakic 2000), monitoring of conflict or errors with respect to behavior and task goals (the anterior cingulate cortex; van Veen et al. 2001), and the cancellation of initiated prepotent behaviors (the right ventrolateral prefrontal cortex; Aron, Robbins, and Poldrack 2004). Robust recruitment in supplementary motor areas is also intriguing, particularly in light of the fact that the contrast included only those trials in which the participant did not smoke. It is possible that recruitment in these areas reflects motor ideation (behavior that was planned but not executed). The high similarity between the identified network of regions and activation reported during inhibitory control tasks like the Stroop (e.g., Bush et al. 1999) provides some support for the suggestion that inhibitory control tasks tap functions that are relevant to voluntary control of drug taking.

### **Differential Craving as a Potential Confound**

There is an experimental confound related to craving in the present study that warrants discussion. The primary contrast subtracted fMRI signal while smoke was not



available from those blocks in which participants voluntarily abstained from smoking. Our goal was to isolate activity recruited by self-control efforts of the participant. However, the two above conditions may have included different levels of craving. If, for example, most self-control trials during which there was strong craving were dropped from this contrast because the participants smoked, then, *all else being equal*, the average craving during Voluntary Abstinence trials would have been lower than that of Smoke Unavailable trials. Alternatively, the availability of cigarette smoke on Self-Control trials may have led to stronger craving on Voluntary Abstinence trials relative to Smoke Unavailable trials; it has, for example, been repeatedly observed that the expectation of imminent smoking increases craving (Carter and Tiffany 2001; Dols et al. 2000, 2002; Juliano and Brandon 1998). If craving differed across conditions, then significant differences in neural recruitment may have reflected differences in craving rather than self-control efforts. We have taken steps to disambiguate these factors in an ongoing larger study using a similar methodology.

### **Taking Stock: What Needs to Be Done**

In our view, the present study demonstrated the feasibility of measuring brain function during a “self-control challenge” in cigarette smokers. However, we did not demonstrate that the brain activity we observed was associated with success in the challenge, much less that it was *causally relevant* to success. There is nothing in the data that were collected that, for example, indicates that higher activation within the prefrontal cortex during Smoke Available trials was associated with a lower rate of smoking. Ongoing research is directed at this question. Assuming such an association is present, of course, still does not establish that observed brain activity is a relevant determinant of the behavior. In order to establish causal influence, it will be necessary to show that the behavior is disrupted by alteration of function in the candidate brain regions. One exciting possibility along these lines is to use repetitive transcranial magnetic stimulation (rTMS) to temporarily “knock out” a targeted brain region. This is feasible for regions on or very near the surface of the cortex. With respect to the brain regions identified in our analysis, certainly the dorsolateral prefrontal region would be a reasonable target for rTMS. It would be interesting to see if voluntary abstinence was reduced when activity in this region was temporarily disrupted.

Even if the above steps were successfully taken, it is important to note that we would not have established that the experimental paradigm described captures the sort of functioning most relevant to actual success in overcoming an addiction. Indeed, we have argued elsewhere (Ainslie 1975, 1992, 2001; Monterosso and Ainslie 2007) that the most critical factor in gaining control over an addiction is the conceived connection between individual temptation and expectation regarding future behavior (e.g., the idea that *this one* tempting cigarette is not really *just this one*, because there is

something more significant in the balance; see chapters 5, 8, and 9 in this volume). The experimental situation that participants were placed in was not likely to engender the cycles of resolution and regret that characterize the real-world struggle of addiction. By instructing participants in such a way as to suggest that it was expected that they would smoke some of the time, participants were likely always in a psychological state that is incompatible with sustained cessation of addiction. For participants in the study, *not smoking* did not take on the status of a personal rule that needed to be followed without fail. That is to say, smoking was maintained as an option throughout. Successfully sustained cessation of an addiction may require that the behavior be seen as off-limits at least most of the time.

The robust prefrontal activity observed during voluntary relative to involuntary abstinence may well reflect the effortful control of attention away from smoking ideation (the imagery of the act that, left unchecked, leads smoothly to its initiation). It has been argued that the essence of willpower involves the skillful direction of attention. Philosopher Michael Bratman (1999) considers the mechanism of willpower to be an avoidance of reconsidering one's resolutions, and this idea dates back to at least William James: "The effort by which [a drunkard] succeeds in keeping the right name unwaveringly present to his mind proves to be his saving moral act" (James 1890, 565). But as we have recently argued elsewhere (Monterosso and Ainslie in press) the control of attention is not itself the essence of willpower, and it probably cannot provide a basis for sustained cessation of drug use because it is not sufficiently reliable over long time periods. Nevertheless, such control may well play a supporting role, increasing the chances of successfully resisting specific challenging temptations when, for whatever reason, resolve is vulnerable. We believe that the reported study represents an initial step toward understanding the dynamics of this control, and that future research efforts in this area can profit from looking at the relationship between brain function and actual behavior during attempts at smoking cessation.

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## Notes

1. First, we performed a rapid localization study in the sagittal plane using gradient echo methods (TR/TE 68/7.5 ms, matrix  $256 \times 128$ , flip angle  $30^\circ$ , FOV 26 cm, 5-mm thickness and gap, scan time 35.6 s) (Frahm, Merboldt, and Hancike 1993). Based on this localizer, we then used an EPI-based shimming procedure (Reese, Davis, and Weisskoff 1995) to establish a typical r.m.s. field uniformity of  $<15$  Hz ( $<0.12$  ppm) over the entire head. Next, two functional runs of the Self-

Control Challenge were acquired using standard gradient-echo EPI scanning (TR = 2000 ms, TE = 45 ms). Data were acquired with 3.125 mm<sup>2</sup> pixels within plane, and with slice thickness of 4 mm with 1 mm skip, acquiring 26 slices. After completion of the test runs, we collected a scan series of high-resolution EPI images (Cohen and Weisskoff 1991) in the same planes (TR 6s, TE 54 ms, 128 × 128 matrix, 20-cm FOV, 4 NEX, scan time 24 s). These T2-weighted images have the same bandwidth and, therefore, the same shape distortions (Cohen and Weisskoff 1991) as the functional data and as such are valuable in providing accurate image registration and localization.

2. Each BOLD time series was motion-corrected using MCFLIRT, part of FSL (FMRIB Software Library) (Smith et al. 2004). The data sets were smoothed with a nonlinear algorithm designed to preserve image structure by only smoothing over voxels classified as the same tissue type (5-mm kernel) (Smith and Brady 1997). Each data set was subjected to a multiple-regression analysis, using a prewhitening technique (Woolrich et al. 2001) to account for the intrinsic temporal autocorrelation of BOLD imaging (Zarahn, Aguirre, and D'Esposito 1997). Z scores and parameter estimates were computed for the comparison of the time course of each intracranial voxel to the HRF-smoothed stimulus waveform using FEAT, part of FSL. Functional data from each run were normalized first to the matched bandwidth high-resolution T2 scan, and then to an FSL standard space template in MNI space.

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