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Common prefrontal regions activate during self-control of craving, emotion, and motor impulses in smokers

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Abstract

It has been posited that self-regulation of behaviors, emotions, and temptations may all rely on a common resource. Recent reviews suggest this common resource may include the inferior frontal cortex (IFC). However, to our knowledge no single functional neuroimaging study has tested this hypothesis. We obtained fMRI scans as 25 abstinent treatment-seeking cigarette smokers completed motor, affective, and craving self-control tasks before smoking cessation treatment. We identified two regions in left IFC and a region in pre-supplementary motor area (preSMA) that were commonly activated in all three tasks. Further, PPI analyses suggest that IFC may involve dissociable pathways in each self-control domain. Specifically, the IFC showed negative functional connectivity with large portions of the thalamus and precentral gyrus during motor stopping, with the insula and other portions of the thalamus during craving regulation, and potentially with a small limbic region during emotion regulation. We discuss implications for understanding self-control mechanisms.

Keywords

smoking; self-control; inhibitory control; emotion regulation; craving; fMRI

Introduction

Successful inhibitory control, or self-control, is key to recovery from addiction, including cigarette smoking. According to Shiffman and colleagues' situational model of relapse (Shiffman, 2005; Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996), the potential for relapse is high across a number of everyday life situations (an argument, sensory cues such as the smell of cigarette smoke, or the offer of a cigarette) that trigger cognitive, affective, and

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motor impulses that can lead people to smoke. Behavioral training designed to teach smokers to successfully navigate these high-risk situations has been the cornerstone of smoking cessation programs for decades. Yet the vast majority of quit attempts end in relapse within one year (Hughes, Keely, & Naud, 2004), largely due to failure of self-control. Thus an improved understanding of the mechanisms underlying self-control is urgently needed, not only to improve the care of over 40 million U.S adults who currently smoke cigarettes (CDC, 2012), but also for those who suffer from other conditions, including substance use and overeating, that involve impairment of self-control.

It has been suggested that self-control of behaviors, emotions, and temptations all rely on a common domain-general resource (Muraven & Baumeister, 2000). This resource is theorized to include regions of the prefrontal cortex (PFC), particularly the inferior frontal cortex (IFC), a region that has been implicated in different types of self-control (Berkman, Burklund, & Lieberman, 2009; Cohen & Lieberman, 2009; Tabibnia et al., 2011). For example, the IFC is activated during motor inhibitory control such as in the stop signal task (Aron & Poldrack, 2006; Leung & Cai, 2007), during cognitive inhibition such as in the color-word Stroop task (Leung, Skudlarski, Gatenby, Peterson, & Gore, 2000) and thought suppression (Mitchell et al., 2007), during emotion regulation (Kim & Hamann, 2007; Ochsner et al., 2004; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008), and during regulation of craving for food and cigarettes (Hartwell et al., 2011; Kober et al., 2010). Although these are distinct regulatory processes (Gross, 2002), they share a common feature, namely that of inhibiting a dominant response. Despite the broad ranging evidence that self-control in different psychological domains activates the IFC, to our knowledge no single functional neuroimaging study has tested whether the IFC may be a common regulatory region across motor, affective, and craving self-control tasks in the same group of individuals. This is an important gap given that everyday situations call for successful regulation across multiple domains.

Although different self-control tasks may recruit the IFC, the downstream regions potentially regulated by IFC could be distinct. The self-control pathway that has been most extensively studied is that of motor inhibitory control. With the help of the pre-supplementary motor area (preSMA) and the subthalamic nucleus (STN), the IFC is thought to enable motor stopping by causing inhibition of the globus pallidus, thalamus, and ultimately the primary motor cortex (M1) (Aron, 2011). In contrast, emotion regulation may involve IFC inhibition of amygdala and subcortical emotion processing regions (Ochsner & Gross, 2005), while regulation of craving may involve an IFC-striatum inhibitory control circuit (Heatherington & Wagner, 2011; Kober et al., 2010). To investigate the extent of overlap in the mechanisms underlying different types of self-control, the current study first tests for common activation of IFC in different self-control tasks and then tests whether the IFC inhibitory control functional connectivity might change depending on the nature of the task (motor, emotion, or craving self-control).

To examine self-regulation in a real-world domain, we tested these hypotheses in a sample of daily smokers who were motivated to quit. Specifically, abstinent smokers underwent functional magnetic resonance imaging (fMRI) as they completed the stop signal task, a task involving cognitive reappraisal of distress, and a task involving cognitive reappraisal of

cigarette craving. Neural response in the IFC, preSMA, and STN were measured in each task, and a conjunction analysis was performed to identify overlapping regions. We hypothesized that IFC would be commonly activated across these three self-control tasks and that the downstream pathways of the IFC would be at least partially distinct in each task.

Methods and Materials

Participants

Twenty-five right-handed adult smokers were recruited as part of the Healthier Brains in Treating Smoking (HaBITS) study (P.I. Tindle), using flier, radio, and newspaper advertisements. Table 1 lists participant details. Exclusion criteria included pregnancy and concurrent substance use, as verified by urinalysis, as well as medication that could affect the nervous system, history of brain injury, cognitive impairment such as dementia, and any untreated psychiatric illness.

Stop Signal Task (SST)

Motor inhibitory control was assessed using the SST (Aron & Poldrack, 2006; Logan, Schachar, & Tannock, 1997). Before scanning, participants completed a practice block of 64 trials (16 Stop trials). The scan-period task consisted of 128 trials (32 Stop trials). Each trial began with a blank screen for a jittered duration (0-2500ms, distributed exponentially), followed by an empty circle (500ms), followed by a left-pointing or right-pointing arrow inside the circle (2000ms). Subjects were to respond as quickly as possible with a left or a right key-press but to stop from pressing if the arrow was followed by a “stop-signal” tone (25% of trials). This signal was presented at a variable delay (the stop-signal delay) after the arrow appeared. After a successful Stop trial, the stop-signal delay was increased by 50ms; after a failed Stop trial, it was decreased by 50ms, eventually titrating to a stop-signal delay resulting in a 50% successful inhibition rate. All subjects reached a 44–56% successful inhibition rate.

Reappraisal Tasks

Craving and emotion regulation were assessed using a modified version of the emotion reappraisal task (Ochsner, Bunge, Gross, & Gabrieli, 2002). The experimental conditions of interest were Look and Reappraise (“Re-Interpret”). A third condition, Mindfully Attend, was also included and discussed in Westbrook et al. (2011). Each trial began with a 2-second instruction screen (“Look”, “Re-Interpret” or “Mindfully Attend”), followed by a fixation cross of jittered duration (0-2500ms, distributed exponentially), followed by a picture for 8 seconds. Using a data-glove (Psychology Software Tools, Pittsburgh, PA), participants then had 4 seconds to rate their craving and 4 seconds to rate their negative emotion, on a 5-point scale (5=strong craving or strongly negative), before viewing a fixation cross for 2 seconds (rest).

There were three types of pictures (distressing, smoking, and neutral). (See Westbrook et al. (2011) and the SOM-U available online.) The neutral pictures were always preceded by the instruction Look; the smoking and distressing pictures were preceded by one of three instructions (Look, Re-Interpret, or Mindfully Attend). On Look trials, subjects were

instructed to passively view the picture. On Re-Interpret trials, they were instructed to reappraise the picture in a neutral manner in order to make it less distressing or less craving-inducing; for example, they could consider a distressing picture to be a scene from a movie or consider a cigarette to be fake or a toy cigarette. The task was presented via E-Prime 2.0 Professional (Psychology Software Tools, Pittsburgh, PA).

Imaging

Scans were performed at the Brain Imaging Research Center jointly established by Carnegie Mellon University and the University of Pittsburgh. Image acquisition and preprocessing procedures are described in the SOM-R available online.

For each participant, each condition (e.g., ReappraiseSmoking) was modeled as an event convolved with the canonical hemodynamic response function. The rest period after instruction was modeled as an explicit baseline, and rests between trials were left unmodeled. Planned comparisons between conditions of interest were computed in SPM8 as linear contrasts. The single subject results were then combined into a random-effects group analysis. To identify activations that overlap in the three self-control tasks, we conducted a 3-way conjunction analysis with the following wholebrain contrasts: StopSuccess > GoSuccess, ReappraiseDistressing > LookDistressing, and ReappraiseSmoking > LookSmoking. Active voxels were those exhibiting above-threshold activation in all 3 contrasts when tested against the conjunction null hypothesis (Nichols, Brett, Andersson, Wager, & Poline, 2005).

To test the neural pathways by which IFC may exert self-control in different domains, psychophysiological interaction (PPI) analyses (Friston et al., 1997) were conducted using the SPM PPI toolbox. For each subject, volumes of interest were extracted from the two IFC clusters identified in the conjunction analysis and used as seeds in single-subject whole brain PPI analyses. These single subject results were combined into group-level t-tests to identify regions exhibiting more negative connectivity with the seed region during the self-control condition (StopSuccess, ReappraiseDistressing, ReappraiseSmoking) compared to the control condition (GoSuccess, LookDistressing, LookSmoking). The SOM-R available online describes the regions of interest and thresholding procedures.

Results

Self-Reported Ratings

As expected, viewing smoking cues increased craving and viewing distressing cues increased distress relative to viewing neutral cues. Smoking cues marginally increased distress but distressing cues did not increase craving relative to neutral cues. As expected, reappraisal of smoking cues and distressing cues reduced the craving and distress, respectively. Reappraisal of smoking cues did not affect distress, and reappraisal of distressing cues did not affect craving (Figure S1 in the SOM-R available online).

Overlap of activation

Each self-control task activated areas previously reported in studies of the SST (Aron & Poldrack, 2006; Leung & Cai, 2007), emotion regulation (Kim & Hamann, 2007; Ochsner et al., 2004; Wager et al., 2008), and craving regulation (Kober et al., 2010), respectively. As depicted in Figure 1, the three tasks elicited similar patterns of activation.

To identify the overlap in activation among the three self-control tasks, we conducted an inclusive 3-way conjunction analysis with the three main contrasts, namely StopSuccess > GoSuccess, ReappraiseSmoking > LookSmoking, and ReappraiseDistressing > LookDistressing. The conjunction analysis identified three clusters: one centered at left IFC *pars triangularis* (IFCtri) and middle frontal gyrus, one centered at left IFC *pars orbitalis* (IFCorb), and one centered at preSMA (Figure U1 in the SOM-U available online). A wholebrain conjunction analysis also identified only these three clusters as overlapping among the three tasks.

PPI: Functional connectivity

To identify neural regions that were functionally connected with the two IFC regions identified in the conjunction analysis, we conducted two separate sets of PPI analyses: one using the IFCorb cluster as a seed and the other using the IFCtri cluster as a seed.

As listed in Table S1 in the SOM-R available online, the IFCorb showed greater negative functional connectivity during StopSuccess than GoSuccess with a number of regions including left ventrolateral thalamus and bilateral precentral gyrus. In other words, when the IFCorb was more active, these regions were concomitantly less active, consistent with the possibility of inhibition by the IFC. During ReappraiseSmoking relative to LookSmoking, there was greater negative functional connectivity of IFCorb with right anterior insula, left middle insula, and ventral anterior thalamus, among other regions. During ReappraiseDistressing relative to LookDistressing, there was greater negative functional connectivity of IFCorb with only two small clusters: left amygdala and left ventral caudate/subcallosal gyrus. These connectivity results were specific to each regulatory task; a conjunction analysis of these three negative PPI analyses indicated no overlapping regions.

As listed in Table S2 in the SOM-R available online, the IFCtri showed greater negative functional connectivity with a number of regions including bilateral precentral gyrus, bilateral thalamus, and left globus pallidus during StopSuccess than GoSuccess. No regions showed greater negative functional connectivity with IFCtri during ReappraiseSmoking than LookSmoking. During ReappraiseDistressing relative to LookDistressing, only the posterior thalamus showed greater negative functional connectivity with IFCtri. A conjunction analysis of these three negative PPI analyses indicated no overlapping regions. (For positive PPI results, see Tables U4 and U5 in the SOM-U available online).

Discussion

This study identifies two regions in left IFC and a region in preSMA that were activated in smokers during performance of self-control tasks across motor, affective, and craving domains. The three regions were the only clusters that were commonly activated across all

three tasks. These results are consistent with meta-analytic reports that regulation of motor, affective, and craving impulses involve a common neural network in addiction (Li & Sinha, 2008). Our findings extend prior work by demonstrating this commonality in the same people across multiple tasks, suggesting that IFC may be a common domain-general region for regulating emotion, craving, and motor impulses. They also provide a functional neural basis for the previous finding that greater IFC gray matter intensity is associated with better motor inhibitory control and emotion regulation (Tabibnia et al., 2011). The additional observations that methamphetamine-dependent individuals exhibit deficits in these self-control tasks and in IFC gray matter intensity, and that lower IFC gray matter is associated with increased drug craving (Tabibnia et al., 2011), further highlight the importance of this region in substance-dependence.

We also found that the IFC involves non-overlapping pathways of regulation during different forms of self-control. Specifically, the IFC showed negative functional connectivity with large portions of the thalamus and precentral gyrus during motor stopping, with the insula and other portions of the thalamus during craving regulation, and potentially with a small limbic region including amygdala and subcallosal gyrus during regulation of distress.

Previous studies have demonstrated overlap of prefrontal activation during individual non-affective self-control tasks. For example, several studies have reported common activation of IFC between motor inhibitory control and suppression of distracting information in the flanker task (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Wager et al., 2005) or set shifting in the Wisconsin Card Sorting Task (Konishi et al., 1999). Ochsner et al. (2009) found overlap of activation in IFC and preSMA during suppression of semantic versus affective information in modified flanker tasks. The affective flanker task did not involve emotion regulation but rather suppression of a response to one affective stimulus in favor of another affective stimulus.

The two IFC clusters activated during self-control in the current study are consistent with prior reports. Activation has been shown in both IFCorb and IFCTri in both hemispheres during motor stopping (Aron & Poldrack, 2006; Chikazoe, Konishi, Asari, Jimura, & Miyashita, 2007; Leung & Cai, 2007; Rubia et al., 2001) and during regulation of negative emotional response (Kim & Hamann, 2007; Lieberman et al., 2007; Ochsner et al., 2002; Ochsner et al., 2004). Left IFCorb and IFC *pars opercularis*, were activated during a craving regulation technique that involved thinking about the long-term consequences of smoking (Kober et al., 2010). Similarly, in a test of behavioral self-control involving a smoking apparatus in the fMRI environment, abstinent smokers who refrained from inhaling the available smoke activated IFCorb and IFCTri (Monterosso et al., 2009).

The current study explored the regulatory pathways from IFC with PPI analyses. Based on these analyses, it seems that the IFCorb, rather than the IFCTri, could be primarily driving the regulation of downstream cortical and subcortical regions during self-control across tasks. Our finding that IFCorb activity is more negatively correlated with activity in thalamus and precentral gyrus during StopSuccess than during GoSuccess is consistent with the proposed pathway of motor inhibition from IFC to M1 (Aron, 2011; Chambers, Garavan,

& Bellgrove, 2009). Consistent with our PPI results in ReappraiseDistressing>LookDistressing, previous studies have demonstrated an inverse relationship between IFCorb and amygdala activity during regulation of negative emotions (Lieberman et al., 2007; Wager et al., 2008). Although to our knowledge no previous study has demonstrated an inverse relationship between IFC and insula activity during craving regulation, insula would be a plausible target for down-regulation, given its critical role in craving, including cigarette craving (Craig, 2009; Naqvi, Rudrauf, Damasio, & Bechara, 2007).

Undoubtedly, brain regions other than IFC play an important role in self-control as well. For example, the preSMA and dorsomedial PFC in general have been implicated in self-control across myriad neuroimaging and lesion studies (Nachev, Kennard, & Husain, 2008). In the current study, the preSMA was identified, along with the IFC, as a common region for different types of self-control. Although the precise functional role of this region in self-control is still unclear, some have suggested that the preSMA may generate the control signal, while the IFC implements it (Aron, 2011).

Although craving induction often increases negative affect and distressing cues often increase craving, that is not always the case (e.g., Shiffman et al., 2013). Given the generally low levels of cue-elicited craving and distress reported by our participants and others (Shiffman et al., 2013), it is possible that more evocative or personalized cues would be more effective in eliciting affective and motivational states. Our findings that reappraising distressing cues does not reduce craving and reappraising craving cues does not reduce distress may seem to contradict the general-domain model of self-control, which predicts that any kind of reappraisal will activate the common self-control network and therefore have some “spillover” effect of incidentally reducing other affective/motivational states as well (Berkman et al., 2009; Verbruggen, Adams, & Chambers, 2012). However, it is plausible that reappraisal spills over only when there is at least a moderate level of craving or distress (i.e., when there is a strong need for reappraisal). Considering the low levels of craving and distress evoked by our stimuli, we may not have been able to detect this process if it occurred.

Limitations

One limitation of the current study is that it lacked a condition in which participants engaged in reappraisal after presentation of neutral stimuli. Without this control, it is difficult to determine whether the self-control processes attenuated general levels of craving/distress or cue-specific levels. Nonetheless, our current results are consistent with the notion that reappraisal of evocative cues does not reduce general levels of craving and distress. If reappraisal were reducing general levels of craving and distress, reappraisal of distressing cues should have reduced craving and reappraisal of smoking cues should have reduced distress. However, we did not observe these effects.

Reporting a relationship between brain activation and behavioral indices of self-control would bolster the claim that a neural substrate of self-control has been identified. However, with $n=25$, our study is underpowered to detect small or moderate brain-behavior correlations. Additionally, the current results could be strengthened by using machine

learning techniques to assess patterns of activity rather than overlap in activity based on traditional univariate analyses.

Implications and Conclusions

The finding that common regions of the IFC are involved in different kinds of self-control supports the popular (albeit understudied) “common resource” account of self-control (Muraven & Baumeister, 2000). When this common resource breaks down, there may be consequences across multiple domains, offering one possible reason for the observed comorbidity of substance use and disorders of mood and anxiety (Lasser et al., 2000). Tasks included in the current study are highly relevant to real-life domains in which treatment-seeking smokers desire greater self-control, including regulating craving and inhibiting motor behavior. One important question raised by this work is whether the observed effects indicate a common resource for smokers specifically, or whether they generalize to other clinical populations (e.g., dieters) and healthy populations in self-regulatory contexts.

Psychotherapies that attempt to enhance patients’ self-regulation skills, such as cognitive-behavioral therapy and interpersonal psychotherapy, do alter function in PFC regions that include IFC (Frewen, Dozois, & Lanius, 2008). The current study assessed participants at baseline only, but future studies will need to test whether these laboratory measures of control (and the common IFC resource) predict future ability to resist temptations to smoke, successfully quit smoking, and achieve other clinical outcomes (Berkman & Falk, 2013). In fact, structural and functional integrity in IFC could be neural markers or endophenotypes for disorders of self-control, potentially allowing for more accurate methods of diagnosis (Bearden & Freimer, 2006) and better predictors of treatment outcome (Berkman, Falk, & Lieberman, 2011).

Another question raised by the current findings is whether engaging in self-control training in one domain (e.g., regulation of craving) can facilitate successful self-control in another domain (e.g., regulation of negative affect) in smokers. For example, improving motor inhibitory control with practice can reduce risky financial decisions (Verbruggen et al., 2012) and reduce emotion-related brain activation (Berkman et al., 2009). Whether such training and “cross”-domain application can be achieved in smokers is a topic for future study.

Tobacco use is the leading cause of preventable disease and death in the United States (CDC, 2012), accounting for about one fourth of the deaths among U.S. adults. Given that failure to regulate negative affect and cigarette craving are major barriers to long term abstinence (Shiffman & Waters, 2004), understanding the neural underpinnings of self-control may offer insights to identifying individuals who are likely to have greater difficulty quitting, and may help inform future cessation interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Table 1**Participant characteristics**

This study was approved by Internal Review Boards at University of Pittsburgh and Carnegie Mellon University and was conducted in accordance with the World Medical Association Declaration of Helsinki. All participants smoked at least 10 cigarettes a day and reported a strong desire to quit and a willingness to participate in smoking cessation classes. Scanning was conducted prior to treatment, following 12-hour abstinence from smoking. Abstinence was validated using a carbon monoxide monitor (Bedfont, Rochester, UK). Participants also performed a urine screen for cocaine, THC, methamphetamine, and opioids. Those who tested positive for any substance were rescheduled; three failures resulted in removal from the study.

Age [M (s.d.)]	42 (12.64)
Sex (% female)	52
Race (%)	
African-American	76
Caucasian	24
Other	0
Annual Income (%)	
<\$20,000	52
\$20,000-50,000	20
\$50,000-75,000	24
>\$75,000	4
Beck Depression Inventory II	
Score [M (s.d.)]	5.52 (4.47)
Scored 13 (%)	88
Smoking Status [M (s.d.)]	
Nicotine dependence (FTND)	4.80 (2.04)
Cigarettes per day	17.83 (6.51)
Years of smoking	24.96 (11.70)
Baseline CO level (parts per million)	14.56 (7.73)