Published in final edited form as:
Psychol Addict Behav. 2013 June ; 27(2): 466–476. doi:10.1037/a0027055.

Neural Correlates of Self-Focused and Other-Focused Strategies for Coping with Cigarette Cue Exposure

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Abstract

Brain imaging research has begun to characterize the neurocognitive processes that cigarette smokers utilize to cope with cue-elicited craving. Presently, however, it remains unclear whether distinct neural substrates support different types of coping. We sought to address this knowledge gap by examining neural responses associated with self-focused and other-focused coping techniques. Fifty-seven treatment-seeking male cigarette smokers initiated an attempt to quit smoking and subsequently underwent functional magnetic resonance imaging, during which they were asked to hold and view neutral cues and a cigarette. Participants were instructed to engage in either self-focused or other-focused coping while being presented with the cigarette and an opportunity to smoke. Those who were told to engage in self-focused coping, but not those told to utilize other-focused coping, exhibited significant activation of several regions previously implicated in self-referential processing, including the medial PFC, precuneus, and insula. In addition, coping strategy modulated the relationship between cigarette-related brain activation and self-reported craving in a subset of these regions. These findings indicate that coping strategies that entail the generation and maintenance of self-relevant information rely upon different psychological and neurobiological mechanisms than those that are not self-focused, even when the latter incorporate information that is very similar in content. Results extend previous work examining the neural substrates of coping with craving. Given the potential mnemonic and motivational advantages associated with self-related processing, findings may have significant implications for selecting and improving techniques for helping quitting smokers resist the urge to smoke.

Keywords

coping; craving; functional magnetic resonance imaging; self; smoking

Relapse remains the unfortunate outcome for the vast majority of individuals who attempt to quit smoking cigarettes (Piasecki, 2006). Smokers are particularly vulnerable to relapse when they encounter cigarette-related stimuli (Ferguson & Shiffman, 2009). Smoking cues are thought to be problematic largely because they elicit a strong urge or craving to smoke (Sayette & Griffin, 2010). Consistent with this view, several studies have established a link between cue-elicited craving and relapse (Ferguson & Shiffman, 2009).

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Research also indicates that the likelihood of relapse during high-risk situations (e.g., when craving is elevated) can be reduced significantly through the use of strategies for coping with craving (Ferguson & Shiffman, 2009). Among the coping strategies that are used, cognitively-oriented techniques (e.g., thinking about the benefits of quitting) often are employed successfully by quitting smokers when urges arise (e.g., Bliss, Garvey, & Ward, 1999). Cognitive coping methods are not fail-safe, however, as quitting smokers often succumb to temptation during high-risk situations despite reporting their use (e.g., Shiffman et al., 1996). Presently, little is known about why cognitive coping strategies are effective in some situations but ineffective in others, primarily because the mechanisms through which they operate remain unclear.

In an important step towards addressing this knowledge gap, researchers have begun to identify the neurocognitive processes involved in the regulation of craving (Brody, et al., 2007; Hartwell, et al., 2011; Kober, et al., 2010; Volkow, et al., 2010). These studies indicate that the modulation of craving involves many of the same brain regions that have been implicated in the regulation of affective states more generally (Davidson, Fox, & Kalin, 2007; Ochsner & Gross, 2005). In particular, the inhibition of cue-elicited responses has been associated with increases in the activation of brain areas supporting domain-general control processes and decreases in the activation of areas supporting more circumscribed affective processes (Brody, et al., 2007; Kober, et al., 2010; Volkow, et al., 2010).

We sought to further elucidate the mechanisms underlying coping by using functional magnetic resonance imaging (fMRI) to examine the neural responses associated with different forms of cognitively-oriented coping. Specifically, we compared a strategy that involved focusing upon the personal benefits of quitting (e.g., "I will breathe easier if I stop smoking") to an approach that entailed focusing on information that was very similar in content but that was directed at another individual (e.g., "My son will breathe easier if I stop smoking"). These strategies were chosen for three reasons. First, similar techniques are employed spontaneously by quitting smokers (O'Connell, et al., 1998) and are taught in formal coping skills interventions (Monti & Rohsenow, 1999). Second, there is reason to predict that different mechanisms may be involved in coping that incorporates self-referential information, relative to coping that is not self-focused. Specifically, a network of brain regions (e.g., medial prefrontal cortex [PFC]) appears to be involved preferentially in the processing of self-related information (Northoff, Qin, & Feinberg, 2011), perhaps even relative to information about close others (Heatherton, et al., 2006). Finally, the different mechanisms supporting self-focused and other-focused coping strategies might influence their effectiveness. For instance, extensive research indicates that information is better remembered and more robust to distracters if it is related to the self than if it is processed in other ways, including by relating it to intimate others (e.g., associating it with a close friend; Symons & Johnson, 1997). Thus, determining whether self-referential versus non-self-referential coping strategies rely upon distinct processes may have significant clinical implications.

Smokers who were motivated to quit were instructed to engage in self-focused or other-focused coping during cue exposure and were given the option of smoking during the study. This manipulation was designed to create conflict between the intention to abstain and the desire to smoke. To our knowledge, this is one of the first studies to examine cue-reactivity in smokers with conflicting motivations for and against smoking *and* a concomitant opportunity to smoke (see also Wilson, Sayette, & Fiez, in press). We anticipated that this tension might lead to a complex pattern of responses (Wilson, Sayette, & Fiez, 2004). In particular, we expected that self-reported urge may be influenced by coping, which presumably would attenuate craving if successful. Importantly this urge appraisal-coping sequence is likely to occur very rapidly, rendering it nearly impossible to capture adequately in real time using a self-report instrument (Lazarus & Folkman, 1984). A feature of the present study is its inclusion of fMRI, which can measure these fleeting processes as they unfold in real time. That is, we believe that fMRI is especially well-suited for uncovering differences between coping strategies that may be difficult to detect via self-report.

Method

Participants

Male smokers (n = 60) were recruited through media advertisements. Usable data were collected from 57 participants (three were excluded due to excessive movement during scanning). Participants were required to be right-handed native English speakers between the ages of 18 and 45 and to have smoked at least 15 cigarettes per day for 24 months. Additionally, they had to report that they were planning on quitting smoking within two weeks, were interested in smoking cessation treatment, and were willing to initiate a quit attempt during the experiment. Participants were randomly assigned to two coping strategy conditions (*self-focused* and *other-focused*; described below). Groups did not differ in age (M = 33.6 years, SD = 8.5), ethnicity (59% Caucasian, 39% African-American, 2% other), cigarettes/day (M = 20.9, SD = 6.0), or nicotine dependence, as assessed using the Fagerström Test for Nicotine Dependence (M = 4.9, SD = 1.6; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991).

Design and Overview

Participants completed two sessions during the study, which are described in detail below. Those deemed eligible based upon a telephone screening were scheduled for an initial baseline session during which questionnaires, behavioral working memory assessments, and coping strategy training were administered. Participants then were scheduled for the fMRI-based experimental session (held within two weeks of the baseline session), during which they performed a working memory paradigm and cue exposure/coping task while fMRI data were collected. The experimental session was scheduled to coincide with the first day of an attempt to quit smoking. Specifically, participants were instructed to initiate a cessation attempt 12-hrs prior to the onset of the experimental visit.

Materials

Questionnaires—During the baseline session, participants completed questionnaires measuring the following: current and past smoking practices (Shiffman, Paty, Kassel, Gnys, & Zettler-Segal, 1994), level of nicotine dependence (Fagerstrom Test for Nicotine Dependence; Heatherton, et al., 1991; Nicotine Dependence Syndrome Scale; Shiffman, Waters, & Hickcox, 2004), smoking abstinence self-efficacy (Relapse Situation Efficacy Questionnaire; Gwaltney, et al., 2001), self-consciousness (revised Self-Consciousness Scale; Scheier & Carver, 1985), trait self-control (Self Control Scale; Tangney, Baumeister, & Boone, 2004), trait positive and negative affect (Positive and Negative Affect Schedule [PANAS]; Watson, Clark, & Tellegen, 1988), and tendency to respond in a socially desirable manner (Balanced Inventory of Desirable Responding Version 6; Paulhus, 1991). In order to measure the effects of nicotine withdrawal on cognitive and emotional functioning, participants completed questionnaires measuring the following at the beginning of Session 2 (i.e., after abstaining from smoking for 12 hours): current levels of positive and negative affect (state version of the PANAS; Watson, et al., 1988) and mental energy/fatigue (State Self-Control Capacity Scale; Ciarocco, Twenge, Muraven, & Tice, 2007). Questionnaire data are not a focus of the present study and are not presented herein.

Cue Exposure/Coping Task—Participants completed a cue exposure procedure adapted from prior research (Wilson, Sayette, Delgado, & Fiez, 2005; Wilson, et al., in press). Runs began with a 48-sec resting baseline. Next, an object was placed in their left hand and prerecorded instructions identifying the object were delivered via intercom. Participants held and passively viewed the object for 74-sec. Participants were able to see what they were holding by way of a live video feed. Participants completed three runs, during which they held a notepad (practice), roll of tape (control cue), and cigarette in the first, second, and third run, respectively. Because exposure to smoking cues can affect responses to subsequently presented items (see Sayette, Griffin, & Sayers, 2010), the order was fixed in this sequence. The first run served as practice and was excluded from analyses. Before the third run, participants were informed that they would hold a cigarette. They were instructed to begin implementing the relevant coping strategy as soon as the cigarette was placed in their hand and to continue doing so until the run concluded. Participants also were told that they would be removed from the scanner and given an opportunity to smoke immediately following the run. Upon presentation of the cigarette, a prerecorded message was delivered informing participants that they would be removed from the scanner and would be able to smoke if they chose to do so.

Urge and Affect—Participants verbally rated their urge to smoke from 0 (*absolutely no urge to smoke at all*) to 100 (*strongest urge to smoke I've ever experienced*) and their affect from 0 (*I feel very bad right now*) to 10 (*I feel very good right now*). These single-item scales have proven sensitive to a range of craving-related experiences (e.g., Sayette, Martin, Hull, Wertz, & Perrott, 2003).

Working memory tasks—Participants completed behavioral working memory assessments and an fMRI-based working memory task (a verbal n-back task adapted from Ravizza, Delgado, Chein, Becker, & Fiez, 2004) as a part of larger study examining individual differences in working memory functioning in individuals who smoke. Results will be presented in a separate manuscript.

Procedure

Baseline assessment/training session—Participants completed a baseline session during which they provided a carbon monoxide (CO) sample and completed questionnaires. After completing questionnaires, participants underwent a behavioral coping strategy training procedure. The training protocol integrated aspects of established coping skills interventions (Monti & Rohsenow, 1999) with procedures that have been successfully implemented in basic behavioral and neuroscientific affect regulation research (Ochsner, et al., 2004). As noted above, participants were randomly assigned to two coping strategy conditions (*self-focused* and *other-focused*). Those in the self-focused condition were trained to generate and maintain thoughts about the positive effects that quitting smoking would have on them personally. Participants in the other-focused condition were trained to generate and maintain thoughts about the positive effects that quitting smoking would have on a specific individual with whom they were close.

During training, participants received explicit instruction and guidance regarding the performance of the strategy that they were to implement in the experimental session. First, participants read a brief description of the relevant strategy. Participants subsequently completed several practice trials during which they were asked to attempt to implement the appropriate strategy while being presented with smoking-related pictures previously shown to elicit robust increases in craving (Mucha, Geier, & Pauli, 1999). Following the completion of each practice trial, participants were asked to record what they had been thinking about during the presentation of the smoking-related picture. This material was reviewed by an experimenter who assessed their performance and helped shape their use of the coping technique as necessary. The experimenter also instructed participants not to use other strategies when performing the practice trials. All participants were judged to have effectively learned the relevant strategy based upon a qualitative assessment made the experimenter.

After training, participants were scheduled for the experiment. They were told to refrain from using nicotine-containing products for at least 12-hr before arrival. In order to model the early phases of cessation, the experiment was scheduled to begin 12-hr after participants had initiated a quit attempt, as noted above.

Experimental session—Upon arrival for the experiment, participants reported the last time they smoked and CO was measured to check compliance with deprivation instructions. Participants had to have a CO level that was at least 50% lower than their baseline, a cutoff established based upon research using similar samples and procedures (e.g., Sayette, Loewenstein, Griffin, & Black, 2008). Participants then provided pre-cue-exposure ratings of urge and affect.

Participants next were informed that they would be given a break during the study, at which point they would have the opportunity to smoke a cigarette, and then were placed in the scanner. After collection of anatomical images, participants completed a working memory task and then the cue exposure/coping procedure. Additional urge and affect ratings were collected immediately following the second and third runs of the cue exposure task while participants were still holding the tape and cigarette, respectively. Subsequently, participants were removed from the scanner and were presented with the opportunity to smoke (those who chose not to smoke were permitted to take a break). After smoking or taking a break, participants completed post-task questionnaires and were given an opportunity to participate in a follow-up study. Finally, participants were debriefed and paid.

fMRI data acquisition—Scanning was conducted using a 3-Tesla head-only Siemens Allegra magnet. A 40 slice oblique-axial anatomical series (3.125 × 3.125 × 3.0 mm voxels) was acquired using a standard T2-weighted pulse sequence. Additionally, a high-resolution (1 × 1 × 1 mm voxels) structural volume was collected using a magnetization-prepared rapid gradient-echo sequence. Functional images were acquired in the same plane as the 40-slice anatomical series with coverage limited to the 38 center slices using a one-shot echo-planar imaging pulse sequence [TR = 2000 ms, TE = 25 ms, FOV = 20 cm, flip angle = 79°]. Heart rate (HR) was recorded during the acquisition of fMRI data using pulse oximetry from the right middle finger.

fMRI data analysis—Preprocessing and analysis of fMRI data was conducted using utilities from the following software packages: Analysis of Functional NeuroImages (version 2.6; Cox, 1996), Automated Image Registration (version 3.08; Woods, Cherry, & Mazziotta, 1992), FMRIB's Software Library (FSL, release 4.1; Smith, et al., 2004), and the NeuroImaging Software Package (version 3.5; Laboratory for Clinical Cognitive Neuroscience, University of Pittsburgh, and the Neuroscience of Cognitive Control Laboratory, Princeton University). Software integration and image format conversion was implemented using the Functional Imaging Software Widgets graphical computing environment (Fissell, et al., 2003). A series of preprocessing steps were employed to correct for artifacts and to account for individual differences in anatomy prior to analyzing fMRI data. Functional images were corrected for head motion and adjusted for drift within and between runs. Participants exhibiting movement that exceeded 3 mm or 3° were excluded from subsequent analysis (three participants were excluded on this basis, as noted above). Anatomical images from each participant were co-registered to a common reference anatomy using a six-parameter rigid-body automated registration algorithm and the transformation matrix generated during this step then was applied to the participant's functional images. Subsequently, functional images were globally mean-normalized and smoothed using a three-dimensional Gaussian filter (4-mm full width at half maximum). Group-based statistical maps were transformed into MNI stereotaxic space (FSL's MNI 152; T1, 1 × 1 × 1 mm) for anatomical localization.

The following steps were used to analyze data from the cue exposure/coping task. First, predictors for each cue type (i.e., control and cigarette) were entered into a general linear model to obtain beta weights for each participant. As in previous work (Wilson, et al., 2005), data collected during the final 48-sec of the control and cigarette cue epochs were included in analyses; data collected during the initial 26-sec were excluded to allow for stabilization of responses associated with prerecorded object identification messages. Beta weights were divided by the estimated run baseline to convert them to units of percent change and were entered into a second-level 2 (coping strategy) × 2 (cue) mixed-model ANOVA. We also examined the relationship between activation during cigarette cue exposure and other cue-reactivity measures (self-reported urge, HR) using whole-brain multiple regression with three covariates: coping strategy (dummy coded), the relevant cue-reactivity measure (self-reported urge or HR; mean centered), and the coping strategy by cue-reactivity interaction (product of the coping strategy and urge/HR covariates).

Monte Carlo simulations indicated that a combined per-voxel threshold of $p < .005$ and cluster-extent threshold of 11 or more contiguous voxels would yield a corrected cluster-wise false positive rate of $p < .05$. These parameters were applied to all statistical maps.

Results

Smoking Behavior and Quit Interest

Five participants in the self-focused condition and eight participants in the other-focused condition chose not to smoke during the experiment; the remaining 44 participants smoked when given the opportunity to do so. The relationship between coping strategy and choice was not significant [$\chi^2(1, N = 57) = .77, p > .5$]. Participants rated their current interest in quitting at the conclusion of the experiment from 1 (*not at all interested*) to 10 (*extremely interested*). Ratings from two participants were missing; results include data from the remaining 55. Participants in the self-focused ($M = 8.42$, $SD = 1.27$) and other-focused ($M = 8.83$, $SD = 1.20$) conditions did not differ in their reported interested in quitting, $t(53) = 1.22$, $p > .2$, $\eta^2 = .03$.

Urge and Affect

Mean urge and affect levels are presented in Table 1. A 2 (coping strategy) × 3 (time) mixed-model ANOVA with the three urge ratings as a repeated variable did not yield significant effects (p's > .2). Similarly, an ANOVA conducted with self-reported affect as the dependent measure did not produce significant results (p's > .2).

Unlike most prior smoking cue-reactivity studies, participants in this study were motivated to quit smoking and were asked to engage in coping during cue exposure. We speculated that a significant proportion of participants may not have exhibited significant increases in urge because of these unique methodological features (i.e., because coping was effective or because they were reluctant to report high levels of urge; see Wertz & Sayette, 2001). As presented in Table 2 and Figure 1, we observed substantial variability in cue-elicited self-reported urge, with similar patterns exhibited by both coping conditions. In order to explore the possibility that some participants may have been reluctant to endorse elevated craving, we examined the relationship between self-reported urge during cigarette cue exposure and scores on a questionnaire assessing the tendency to respond in a socially desirable manner (Balanced Inventory of Desirable Responding Version 6 [BIDR-6]; Paulhus, 1991). Craving ratings provided at the conclusion of the cigarette cue exposure period negatively correlated with scores on the BIDR-6 [$r(57) = -.37$, $p < .01$, $\eta^2 = .14$], suggesting that urge ratings may have at least in part reflected demand characteristics associated with the study (cf. Sayette & Parrott, 1999).

Heart Rate

Due to technical error, data were not collected from six participants (five self-focused, one other-focused). Using available data, we conducted a 2 (coping strategy) × 2 (cue) ANOVA, with HR (beats/min) averaged across the time period during which the control and cigarette cues were held as the dependent variable. We observed a significant main effect of cue, with greater HR during the cigarette cue than the control cue, $F(1, 49) = 7.84$, $p < .01$, $\eta^2 = .14$ (see Table 1). None of the remaining effects were significant.

fMRI Results

Main effect of cue—Regions exhibiting a main effect of cue are presented in Table 3. Activation was greater during the presentation of the cigarette cue than the control cue in several areas, including the PFC, anterior and posterior cingulate, thalamus, and cerebellum. Greater activation during the control cue relative to the cigarette was observed in the superior temporal gyrus bilaterally.

Coping strategy x cue interaction—A significant coping strategy by cue interaction was observed in several regions implicated in self-referential processing, including midline cortical structures (medial PFC, dorsal and rostral anterior cingulate [ACC], and precuneus) and the insula bilaterally (see Table 4 and Figure 2). The large medial frontal region that exhibited a coping strategy by cue interaction partially overlapped with a midline region that showed a main effect of cue. (Specifically, 12% of the voxels in the medial PFC/dorsal ACC demonstrating a main effect also displayed an interaction.) The effect of cue was examined separately for the self-focused and other-focused conditions to characterize the interaction for each region. As presented in Table 4, activation during the cigarette cue was greater than that during the control cue for participants in the self-focused condition in each region. In contrast, activation during the control cue either did not differ from or was significantly greater than activation during the cigarette cue for participants in the other-focused condition in these areas.

Modulation of activation/cue-reactivity correlations by coping strategy—A significant relationship between cigarette-related activation and urge ratings during cigarette cue exposure was observed in the right superior frontal gyrus (MNI coordinates × = 26, y = −2, z = 62; Brodmann Area [BA] 6; size = 322 mm^3; average F ratio = 11.76) and right dorsolateral PFC (x = 52, y = 33, z = 14; BA 46; size = 322 mm^3; average F ratio = 10.89). Considering the sample as a whole, greater activation was associated with lower self-reported urge to smoke during cigarette cue exposure for both ROIs. For each region, however, this relationship was driven by a robust negative association between cue-elicited urge and brain activation for the other-focused group [right superior frontal gyrus: $r(29) = -.64$, $p < .001$, $\eta^2 = .41$; right dorsolateral PFC: $r(29) = -.63$, $p < .001$, $\eta^2 = .40$]. In contrast, for the self-focused group, cue-elicited urge was positively related to activation of the dorsolateral PFC [$r(28) = .40$, $p < .04$, $\eta^2 = .16$] and unrelated to activation of the superior frontal gyrus [$r(28) = .27$, $p = .16$, $\eta^2 = .07$].

Of particular interest, a significant relationship between cue-elicited activation and the interaction between coping strategy and smoking urge was observed in the left inferior parietal lobule, bilateral insula, and right inferior frontal gyrus (see Table 5 and Figure 2). As shown in Figure 2, these regions fall close to or overlap with those exhibiting a significant coping strategy by cue interaction (the right insula/inferior frontal gyrus and left insula ROIs identified in the multiple regression analysis overlap with 66% and 16% of the voxels exhibiting a significant coping strategy by cue interaction, respectively). Cue-elicited activation of each region was positively correlated with urge ratings during cue exposure for the self-focused group. In contrast, activation was unrelated to (right insula) or negatively correlated with (inferior parietal lobule, left insula, right inferior frontal gyrus/insula) urge for the other-focused group. (As indicated in Table 5, the effect was marginally significant ($p < .1$) for the left insula and right inferior frontal gyrus/insula.)

We observed a negative correlation between cigarette-related activation and HR during cigarette cue exposure in the right anteroventral PFC for both coping groups (x = 37, y = 46, z = −10; BA 10/47; size = 557 mm^3; average F ratio = 15.68). We also observed a significant relationship between cue-elicited activation and the interaction between coping strategy and HR in the middle and inferior occipital gyri bilaterally (left hemisphere: × = −26, y = −82, z = −9; BA 18; size = 674 mm^3; average F ratio = 10.63; right hemisphere: × = 30, y = −87, z = −1; BA 18; size = 674 mm^3; average F ratio = 11.22; see Figure 2). Cue-elicited activation of both regions was negatively correlated with HR during cue exposure for participants in the self-focused condition, while cigarette-related activation and HR were not related for participants in the other-focused condition.

Discussion

We examined neural activity in quitting-motivated male cigarette smokers engaging in self-focused or other-focused coping while being presented with a cigarette cue and an opportunity to smoke. Several brain regions exhibited significant main effects due to cue exposure. Consistent with previous research, cigarette-related increases in activation were observed for both groups in the middle frontal gyrus (e.g., Due, Huettel, Hall, & Rubin, 2002; McBride, Barrett, Kelly, Aw, & Dagher, 2006), ACC (e.g., Brody, et al., 2007; Wagner, Dal Cin, Sargent, Kelley, & Heatherton, 2011), posterior cingulate (e.g., McClernon, Kozink, & Rose, 2008; Wilson, et al., 2005), dorsal striatum (e.g., McClernon, Kozink, Lutz, & Rose, 2009; Yalachkov, Kaiser, & Naumer, 2009), parahippocampal gyrus (e.g., Janes, et al., 2010; Smolka, et al., 2006) and cerebellum (e.g., McClernon, et al., 2008; Wilson, et al., in press).

Of primary interest, we also found that coping strategy affected cue-related activation in several brain areas. Quitting smokers who were told to focus on the personal benefits of smoking cessation, but not those told to focus on the benefits that cessation would have on someone close to them, exhibited significant cue-related activation of the medial PFC, precuneus, and dorsal and rostral ACC (the dorsal ACC region partially overlapping with an area exhibiting a main effect of cue). These findings are consistent with extensive evidence implicating these midline cortical structures as key brain areas supporting self-referential processing (Cavanna & Trimble, 2006; Heatherton, et al., 2006; Northoff, et al., 2006). Also of note, only the self-focused coping condition was associated with cue-related activation of the anterior insula, a region that has received increasing attention from addiction researchers (Garavan, 2010; Naqvi & Bechara, 2010; Naqvi, Rudrauf, Damasio, & Bechara, 2007) and that appears to play an important role in self-related processing (Craig, 2009; Feinberg, 2011; Northoff, et al., 2011). Presumably, the greater activation of this set of regions (particularly medial cortical structures) by the self-focused relative to the other-focused group reflects the higher degree of self-related processing (e.g., self-focused attention) utilized by the former during cue exposure. Such effects may have important clinical implications, as recent findings suggest that the success of smoking cessation interventions relates to the degree to which they engender a sense of personal relevance, as discussed further below (Chua, et al., 2011; Chua, Liberzon, Welsh, & Strecher, 2009).

We found additional evidence of differences between the coping strategies upon examining the relationship between brain activation and other cue-reactivity measures. For the other-focused group, smoking urge was negatively associated with cue-related activation of the dorsolateral PFC and superior frontal gyrus, regions that recently have been linked to the modulation of craving (Hartwell, et al., 2011; Kober, et al., 2010; Rose, et al., 2011). In contrast, self-reported urge was positively associated with cue-related activation of the dorsolateral PFC, but unrelated to activation of the superior frontal gyrus, for the self-focused group. Divergent associations between cue-elicited urge and brain activation as a function of coping strategy were observed in several additional regions. Specifically, urge was positively related to cue-elicited activation of the left inferior parietal lobule, bilateral insula, and right inferior frontal gyrus for the self-focused group, but negatively correlated with or unrelated to activation of these areas for the other-focused group. Notably, these areas overlap with those that demonstrated a significant coping strategy by cue interaction, suggesting that the different neural activation patterns exhibited by the self-focused and other-focused groups are behaviorally relevant. Effects observed in the insula, which appears to play a critical role in drug craving (Garavan, 2010; Naqvi & Bechara, 2010; Naqvi, et al., 2007), are of particular interest. Further research is needed to determine whether the observed effects are associated with strategy-related differences in the regulation of the interoceptive processes mediated by the insula, differences in the use of such processes in support of coping, or some other mechanism.

Additionally, HR was differentially coupled with the activation of bilateral extrastriate visual cortical regions as a function of coping condition (i.e., cue-elicited activation in the visual cortex was negatively correlated with HR during cue exposure for the self-focused group, while cigarette-related activation and HR were not related for the other-focused group). This result may have clinical significance, as Brody and colleagues (2007) found that treatment-seeking smokers exhibited decreased cue-elicited activation of the visual cortex when they were told to resist their craving, compared to when they were told to allow themselves to crave. Additional research is needed to elucidate the functional significance of this pattern, as cue-elicited changes in HR can reflect a variety of influences (see Carter & Tiffany, 1999; Sayette, et al., 2000)

Taken together, our findings suggest that coping involving the generation and maintenance of self-relevant information rely upon different psychological and neurobiological mechanisms than those that are not self-focused, even when the latter incorporate information that is very similar in content. As noted above, the different processes underpinning self-focused and non-self-focused cognitive coping techniques may have implications for their relative efficacy. Information is better remembered and more robust to distracters if it is related to the self than if it is processed in other ways (Symons & Johnson, 1997). To the extent that such effects extend to the domain of coping, attempting to focus on their personal reasons for quitting may provide a mnemonic advantage relative to trying to think of other potential sources of motivation for those attempting to discontinue smoking. Interestingly, recent studies have found that some of the same regions identified in the current investigation (medial PFC and precuneus/poster cingulate) were more strongly activated by smoking cessation messages that contained personalized material than those containing generic information (Chua, et al., 2009), and that the degree to which such regions were engaged by personally-tailored messages predicted the odds of quitting smoking four months later (Chua, et al., 2011). These findings highlight personal relevance (which may influence motivation to change behavior) as an important factor in determining the success of smoking cessation interventions, offering another potential benefit of self-focused relative to non-self-focused coping strategies (i.e., in addition to the potential mnemonic advantages afforded by the former).

It is important to note, however, that although we have focused on the potential advantages associated with coping that heavily involves self-related processing, we did not find direct evidence that the self-focused and other-focused strategies differed in effectiveness, leaving open the possibility that the strategies were equally efficacious (or even that the other-focused strategy was superior to the self-focused strategy). As noted, the majority of participants in each condition chose to smoke when given the opportunity to do so. In addition, both groups failed to exhibit significant increases in self-reported urge during cue exposure. The lack of self-reported urge effects may relate to key differences between the methods employed in the current investigation and the procedures typically used in prior research. Specifically, participants were asked to engage in coping while being exposed to a cigarette cue in the present study, whereas participants in prior studies generally were not asked to engage in any form of self-regulation. It is possible that the lack of urge increases during cue exposure in the present study may reflect the influence of coping (i.e., which attenuated increases in urge for some). As noted above, this process is likely to occur rapidly (Lazarus & Folkman, 1984), highlighting the utility of fMRI for revealing strategy-related differences that were not detected through the assessment of self-report. The lack of urge effects also may relate in part to the influence of experimental demand (cf. Sayette & Parrott, 1999). Still another possibility is that participants may not have reported increases in urge because they were motivated to quit smoking (see Wertz & Sayette, 2001). Regardless, the significant variability in urge exhibited by participants allowed us to examine relationships between cue-elicited brain activity and craving.

Recent data from our laboratory indicate that quitting smokers do endorse cue-elicited increases in urge, at least under certain conditions. Specifically, in a recent fMRI study utilizing the same cue exposure procedure, quitting-motivated smokers who were told that they could smoke – and were not asked to engage in coping – reported a mean urge level of 77on a 0-100 scale while holding a cigarette, which was significantly greater than the mean urge of 68 that they reported while holding a control cue (Wilson, et al., in press). These results support the idea that coping influenced urge reporting in the current study.

Additional limitations should be mentioned. This study included only male smokers. This decision was based upon research demonstrating that male and females exhibit different patterns of neural activation during the affect regulation (Domes, et al., 2010; McRae, Ochsner, Mauss, Gabrieli, & Gross, 2008) and drug cue exposure (Kilts, Gross, Ely, & Drexler, 2004; McClernon, et al., 2008). We sought to maximize our ability to detect effects of interest by excluding potential sex differences. Additional research is needed to determine whether or not findings generalize to female smokers.

It also is worth noting that, while cue-related activation was observed in several brain areas identified in previous research (see above), we failed to find cue-elicited activation in other regions thought to play an important role in drug addiction, including the amygdala and ventral striatum (Koob & Volkow, 2010). Activation in one or both of these brain areas has been observed in several prior studies (e.g., David, et al., 2005; Franklin, et al., 2009; Franklin, Wang, Li, et al., 2011; Franklin, Wang, Suh, et al., 2011; Franklin, et al., 2007; Stippekohl, et al., 2010). It is possible that the absence of effects in these regions relate to the use of coping by participants in the present study (e.g., see Volkow, et al., 2010). However, given that we failed to observe main effects in these regions in prior studies that did not involve coping (Wilson, et al., 2005; Wilson, et al., in press), it is likely that the discrepancy between our results and prior findings is at least in part due to factors other than coping, such as differences in imaging technique (e.g., blood-oxygen-level-dependent versus arterial spin labeling perfusion fMRI) or cue exposure methods (e.g., the use of a single, relatively static smoking cue versus the use of more dynamic or multiple cues). Future research is needed to explore these possibilities.

Notwithstanding these potential limitations, the present findings highlight the importance of examining the neurocognitive mechanisms supporting different cognitively-oriented coping strategies. In addition to advancing understanding of the coping process, investigating how various coping techniques operate may facilitate efforts to select and improve techniques for helping quitting smokers resist temptation. To our knowledge, this is the first study to demonstrate that self-referential and non-self-referential coping strategies are associated with different patterns of brain activation. By helping to establish key linkages between coping with craving, the emerging neuroscience literature on the neurobiological underpinnings of self-referential processing (Northoff, et al., 2011), and the extensive cognitive psychology literature on self-referential encoding (Symons & Johnson, 1997), the present findings also point towards useful targets for future research. Given the potential mnemonic and motivational advantages associated with self-related processing, additional research utilizing more extensive training procedures to explore the clinical concomitants of self-referential versus non-self-referential strategies for regulating urge may be particularly fruitful. In addition, research exploring factors that may serve to differentially moderate the effectiveness of self-focused relative to non-self-focused coping techniques, such as genetically driven variation in the functioning of regions more strongly linked to one approach to coping than the other (e.g., see Franklin, et al., 2009; Franklin, Wang, Li, et al., 2011), would be useful.

Results from the current study also have important methodological implications. As noted above, naturalistic studies suggest that quitting smokers often spontaneously implement self-referential and non-self-referential coping strategies (O'Connell, et al., 1998). To the extent that the use of such techniques differs across individuals, or across time within individuals, it will be important for researchers to account for coping strategy as a potential source of variance (cf. Hartwell, et al., 2011). More generally, our findings suggests that it is feasible to study cue-reactivity and coping in smokers under conditions that have not previously been investigated in detail. Specifically, an attempt was made to create a high degree of conflict between the intention to abstain and the urge to smoke by selecting participants who were motivated to quit smoking and subsequently presenting them with smoking cues and an opportunity to smoke. The current study provides preliminary support for the idea that this unique motivational state can be produced under controlled laboratory conditions. As the results from such research stand to greatly inform our understanding of the ambivalence associated with addiction and relapse, additional work using this approach is indicated. Finally, this research highlights the utility of brain imaging approaches to capture rapidly emerging processing associated with urge appraisal and coping appraisal that are difficult to assess unobtrusively and in real time using self-report instruments.

Acknowledgments

This research was supported by grant R01 DA02463 from the National Institute on Drug Abuse. This paper is based upon a dissertation completed by S.J.W. Portions of these data were presented at the annual meeting of the Society for Neuroscience (Chicago, November 2009). We thank Michael Pogue-Geile, Ahmad Hariri, and Richard Jennings for helpful discussion. We also are indebted to Deidra Rendinell for assistance with data collection.

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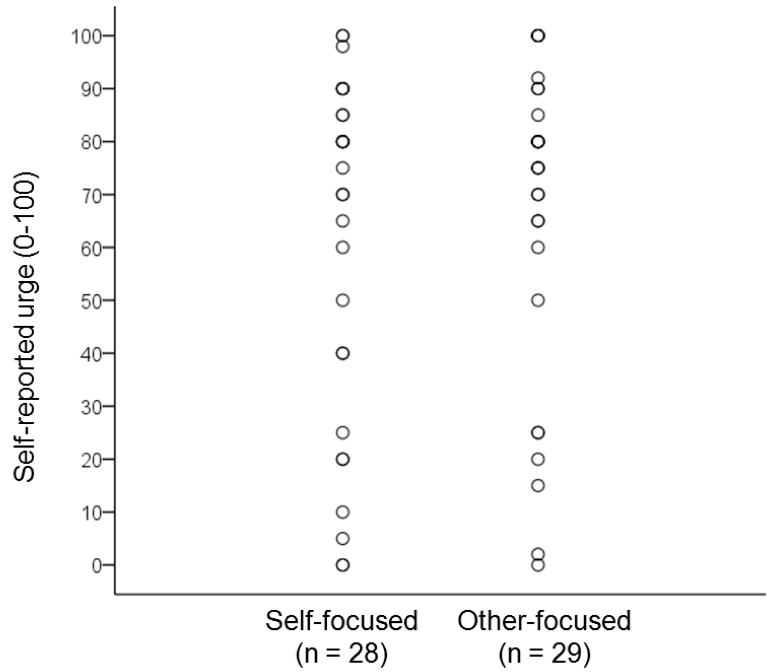

Figure 1.
Scatterplot of self-reported urge during cigarette cue exposure for the self-focused and other-focused groups.

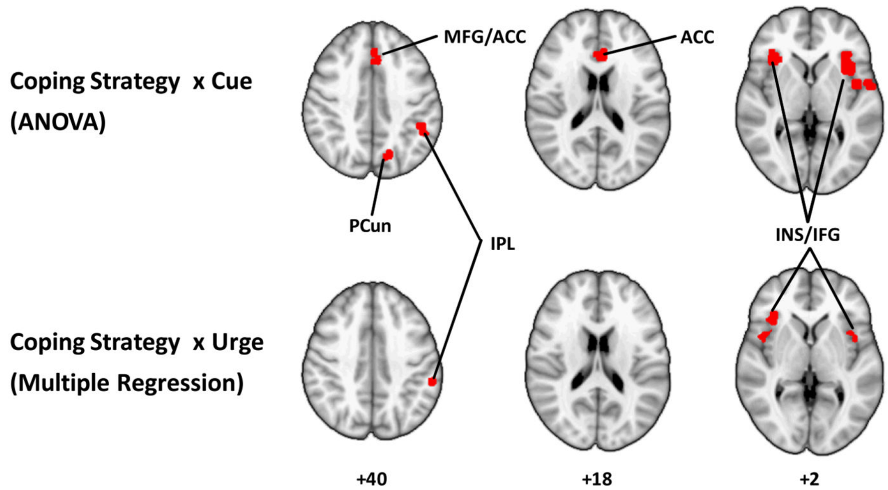

Figure 2.

Row 1: Regions exhibiting a significant coping strategy (self-focused vs. other-focused) by cue (control, cigarette) interaction. Row 2: Regions exhibiting a significant relationship between cigarette-related activation and the interaction of coping strategy and urge to smoke during cigarette cue exposure. The numbers below each column denote the distance (millimeters) of the brain slice from the anterior commissure–posterior commissure plane in MNI stereotaxic space. Brain slices are right-left reversed. Abbreviations: ACC, anterior cingulate cortex; IFG, inferior frontal gyrus; INS, insula; IPL, inferior parietal lobule; MFG, medial frontal gyrus; PCun, precuneus.

Table 1

Mean (SD) for Urge, Affect, and Heart Rate

	Full sample (n = 57)	Self-focused condition (n = 28)	Other-focused condition (n = 29)
Affect-baseline	7.1 (1.7)	7.1 (1.9)	7.0 (1.7)
Affect-control cue	7.0 (2.3)	6.8 (2.7)	7.2 (1.8)
Affect-cigarette cue	7.0 (2.3)	6.7 (2.7)	7.3 (1.9)
Urge-baseline	62.5 (25.7)	64.5 (22.6)	60.6 (28.6)
Urge-control cue	64.3 (28.8)	61.1 (30.2)	67.4 (27.6)
Urge-cigarette cue	64.0 (31.7)	60.6 (33.1)	67.2 (30.5)
Heart rate-control cue	60.2 (8.1)	61.0 (7.9)	59.6 (8.4)
Heart rate-cigarette cue	61.2 (8.6)	61.9 (8.4)	60.6 (8.8)

Note. Heart rate is presented in beats per minute.

Table 2

Percentage of participants reporting an increase, no change, or a decrease in craving during cigarette relative to control cue exposure

	Full sample (n = 57)	Self-focused condition (n = 28)	Other-focused condition (n = 29)
Increase	47	50	45
No change	26	29	24
Decrease	26	21	31

Table 3

Brain Regions Exhibiting a Significant Main Effect of Cue

Region	BA	Size (mm³)	MNI Coordinates x	y	z	Average *F* ratio
Cigarette > Control						
ACC/superior frontal g/SMA	6/32	2168	−4	7	55	12.41
L middle frontal g (dorsolateral PFC)	9	322	−43	3	41	10.76
Posterior cingulate g	29	1260	8	−28	27	9.94
L middle frontal g	10	938	−34	45	25	11.39
R parahippocampal g	34	352	18	−24	−20	12.55
L caudate nucleus/thalamus		1846	−18	−2	20	11.35
R thalamus		586	7	−19	15	10.36
Cerebellum		410	33	−62	−30	12.47
Cerebellum		469	−30	−58	−33	10.49
Control > Cigarette						
L superior temporal g	22	3105	−60	−26	6	14.54
R superior temporal g	22	1289	60	−13	0	13.08

Note. Stereotaxic coordinates are given for local maxima of activation cluster in MNI atlas space. ACC, anterior cingulate cortex; BA, Brodmann's area; g, gyrus; L, left hemisphere; PFC, prefrontal cortex; R, right hemisphere; SMA, supplementary motor area.

Table 4

Brain Regions Exhibiting a Significant Coping Strategy x Cue Interaction

			MNI Coordinates					
Region	**BA**	**Size (mm³)**	**x**	**y**	**z**	**Average *F* ratio**	**Self-focused condition (n = 28)**	**Other-focused condition (n = 29)**
L precuneus	7	439	−12	−69	46	11.17	Cigarette > Control[b]	Control > Cigarette[a]
Medial frontal g/dorsal ACC	8/32	1230	−1	32	45	11.70	Cigarette > Control[b]	Control > Cigarette[a]
L inferior parietal lobule	40	410	−48	−45	36	9.67	Cigarette > Control[b]	ns
L middle frontal g (rostral PFC)	10	615	−37	38	26	10.65	Cigarette > Control[b]	ns
Rostral ACC	24	381	−1	30	6	0.21	Cigarette > Control[b]	Control > Cigarette[a]
R insula/inferior frontal g	13/45/47	527	34	24	6	11.23	Cigarette > Control[b]	ns
L insula/inferior frontal g/superior temporal g	13/47/22	2490	−36	18	0	11.20	Cigarette > Control[b]	Control > Cigarette[b]
Cerebellum		352	−12	−77	−28	9.63	Cigarette > Control[b]	Control > Cigarette[a]

Note. Stereotaxic coordinates are given for local maxima of activation cluster in MNI atlas space. ACC, anterior cingulate cortex; BA, Brodmann's area; g, gyrus; L, left hemisphere; ns, no significant effect of cue; PFC, prefrontal cortex; R, right hemisphere.

[a] $p < .05$.

[b] $p < .01$.

Table 5

Coping Strategy Moderates the Relationship between Brain Activation and Self-Reported Urge during Cigarette Cue Exposure

			MNI Coordinates					
Region	BA	Size (mm^3)	x	y	z	Average *F* ratio	Self-Focused Condition (n = 28)	Other-Focused Condition (n = 29)
L inferior parietal lobule	40	615	−59	−36	33	10.89	Positive[c]	Negative[c]
L insula	13	352	−43	7	2	10.11	Positive[b]	Negative[a]
R insula	13	527	45	10	1	10.30	Positive[c]	Ns
R inferior frontal g/insula	47/13	439	40	24	1	10.56	Positive[b]	Negative[a]

Note. Stereotaxic coordinates are given for local maxima of activation cluster in Montreal Neurological Institute (MNI) atlas space.

Abbreviations: BA, Brodmann’s area; g, gyrus; L, left hemisphere; Negative, negative correlation between brain activation and selfreported urge during cigarette cue exposure; ns, no significant relationship between brain activation and self-reported urge during cigarette cue exposure; Positive, negative correlation between brain activation and self-reported urge during cigarette cue exposure; R, right hemisphere.

[a] $p < .1$

[b] $p < .01$

[c] $p < .001$