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Title

Self-efficacy modulates the neural correlates and self-reported craving in male smokers and ex-smokers: an fMRI study

Running title

Self-efficacy and craving

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Abstract

The regulation of cue-induced craving for cigarettes is a key factor in smoking cessation. Outcomes of smoking cessation have been linked to self-efficacy, faith in one's own ability, in smokers. However, no study has examined the neural basis of self-efficacy during the control of craving. We examined whether self-efficacy can affect the neural response to smoking cues in smokers and ex-smokers using functional magnetic resonance imaging. During scanning, participants were instructed (1) to view smoking-related images passively, (2) to view the smoking-related images with a strategy focused on self-efficacy to control cue-induced craving, or (3) to view neutral images. In smokers, the self-efficacy strategy significantly reduced self-reported craving. This strategy was related to increased activation in the rostral medial prefrontal cortex (rmPFC) and the pregenual anterior cingulate cortex (pgACC) in smokers compared to ex-smokers. Furthermore, smokers showed increased effective connectivity between rmPFC and hippocampus and between pgACC and parahippocampus gyrus when employing the self-efficacy strategy compared to ex-smokers. The magnitude of the rmPFC-hippocampus connectivity was positively correlated with self-reported self-efficacy. Our findings suggest that in smokers, self-efficacy is related to activation and connectivity in brain regions involved in regulating craving and self-assessment. The current study provides evidence for understanding the underlying cognitive and neurobiological mechanisms involved in the control of craving to smoke cigarettes.

INTRODUCTION

In smoking cessation, craving management is essential for success in quitting smoking and preventing relapse (Shiffman et al., 1996). Control of craving is one of the main targets of pharmacotherapy and behavioral therapy for smoking cessation (Clinical Practice Guideline Treating Tobacco et al., 2008). Among the types of craving, cue-induced craving evoked by stimuli (e.g., cigarette-related images and events) may persist for years despite the maintenance of abstinence (Shiffman et al., 2004), which can result in the failure of smoking cessation.

The neural basis of cue-induced craving has been investigated using neuroimaging techniques such as functional magnetic resonance imaging (fMRI). Smoking-related cues elicit activation in brain regions linked to reward, e.g., ventral tegmental area (VTA) and ventromedial striatum (VS) (Due et al., 2002), memory and learning, e.g., hippocampus, parahippocampus gyrus, and amygdala (Robbins *et al.*, 2008), and motivation, e.g., anterior cingulate cortex (ACC) (Brody et al., 2007; McClernon et al., 2008), in smokers (Jasinska et al., 2014). In addition, the magnitude of brain responses to the cues predicts the success rate of quitting smoking (Jasinska et al., 2014).

Clinical studies have shown that some strategies are effective in controlling craving, including distracting from smoking, contemplating the adverse effects of smoking, and employing mindfulness (Clinical Practice Guideline Treating Tobacco et al., 2008). In addition to these, a strategy that focuses on self-efficacy has also been shown to be effective (Bandura, 1997; Brandon et al., 2004). Self-efficacy is defined as faith in one's own ability to abstain from smoking in a craving situation (Bandura, 1977; Condiotte and Lichtenstein, 1981; Gwaltney

et al., 2002). High self-efficacy is associated with a high success rate in quitting smoking and a low relapse rate (Bandura, 1997; Gwaltney et al., 2002; Schnoll et al., 2011). Furthermore, high self-efficacy has been reported to decrease craving (Shadel and Cervone, 2006). Thus, the enhancement of abstinence self-efficacy is emphasized in representative treatment models for smoking cessation, e.g., transtheoretical model (Prochaska and DiClemente, 1984), relapse prevention model (Marlatt and George, 1984), and motivational interview (Miller, 1996).

Although these clinical studies have shown that self-efficacy is important for regulating craving, few studies have investigated the mechanisms that underlie how self-efficacy modulates craving. Self-efficacy requires abilities to develop a concrete plan to achieve a goal, to imagine oneself doing something, and to examine whether one has the ability to follow something through to the end. Thus, self-efficacy itself is, by definition, a complex construct that involves multiple cognitive processes, but the self-assessment process is a key part of self-efficacy (Bandura, 1997). Furthermore, self-efficacy is achieved by multiple sub-strategies or information, including a successful experience, vicarious experience, verbal persuasion, and physiological/affective states. However, a successful experience is the strongest factor of self-efficacy (Bandura, 1977; Elshatarat et al., 2016).

The main aim of our study was to investigate the effects of self-efficacy strategy on the neural correlates of cue-induced craving and those of regulation craving in smokers and ex-smokers. We employed a paradigm where participants were asked to control craving with a strategy

focused on self-efficacy. We hypothesized that self-efficacy would modulate the activation of brain regions involved in self-assessment, i.e., the medial prefrontal cortex (mPFC) (D'Argembeau et al., 2007; Ochsner et al., 2005), and in craving-related regions, i.e., VTA, VS, hippocampal regions, and ACC. We also hypothesized that sub-strategies of self-efficacy, e.g., recall of successful experiences of abstinence, would show differential modulation of brain activation and connectivity between these regions.

METHODS

Participants

Twenty-nine treatment-seeking smokers and 25 ex-smokers were recruited via posters and bulletin board ads in the hospitals and health examination centers of Kyoto University, Osaka Psychiatric Medical Center and the Takeda Hospital Group. All of the participants were right-handed males, mean age 41.3 [standard deviation (SD) ± 9.3] years. We recruited only male participants because of potential gender differences in 1) self-efficacy (Pelissier and Jones, 2006), 2) self-reported craving (Field and Duka, 2004; Perkins, 2009), and 3) brain activity during exposure to smoking-related cues (Potenza et al., 2012; Wetherill et al., 2013). Smokers met the DSM-IV-TR criteria for nicotine dependency (APA, 2000). All participants of the smokers group had smoked at least 10 cigarettes per day. They intended to quit smoking within 6 months and had sought treatment supporting smoking cessation, and exhaled ≥8 ppm carbon monoxide as measured by carbon monoxide monitor (piCO$^+$ Smokerlyzer, Harada Corporation, Osaka, Japan). The inclusion criteria for ex-smokers comprised: individuals who had continually ceased smoking for >6 months, exhaled <8 ppm carbon monoxide at the time of assessment, and met the smoker criteria when they smoked. The exclusion criteria

consisted of a history of head trauma, any neurological illness, serious medical or surgical illness, and other substance abuse. Comorbid disorders and history of any psychiatric disorders were screened using the Structured Clinical Interview for DSM-IV-TR. All participants were physically healthy at the time of the assessments. After a scan and psychological tests, 7000 yen (approximately $60) was paid to each participant. This study was approved by the Committee on Medical Ethics of Kyoto University and performed according to the Code of Ethics of the World Medical Association and the Helsinki Declaration of 1975, as revised in 2013. After complete description of the study, written informed consent was obtained from each participant.

Cue Presentation and Craving Monitoring

Cue presentation consisted of an 8-min session with pseudorandom presentation of 24 smoking-related pictures and 24 neutral pictures in a block design. Each condition was comprised of six task blocks. Each block of four pictures lasted 20 s. Smoking pictures comprised smoking-related objects (e.g., a burning cigarette end, an ashtray, and a smoking person) in a variety of situations where smokers wanted to smoke (e.g., coffee break, drinking, talking with a smoker). Pictures of smoking were purchased from a website (PIXTA, http://pixta.jp/). Neutral pictures contained neutral objects (e.g., a book, a dish, a non-smoking person), which were matched in terms of frequency of occurrence, gender, and body parts with the smoking pictures. We made the visual complexity of neural and smoking pictures as similar as possible except for cigarettes and an ashtray. The neutral pictures were

captured and processed by one of the authors. Prior to a task block, an instruction slide was presented for 2.5 s. Each participant was instructed to imagine quitting smoking and view the pictures as a real situation, and to look at the pictures in different ways depending on the instruction slides, as described in the following. There were three types of instruction slides showing: (1) “feel as you like” required passively viewing smoking images (craving condition); (2) “I can” required viewing smoking images and regulating craving with the idea that “I think I can stay abstinent in the induced craving situation” [regulating with the self-efficacy strategy (regulation condition)]; and (3) a star symbol, which simply required viewing neutral images (neutral condition). After each block, the participants were asked to rate their craving for smoking on a visual analog scale (VAS), ranging from 0 (no craving at all) to 100 (extreme craving) using a joystick (Joystick Fiber Optic Response Pad, Current Designs Inc., Philadelphia, PA, USA). If the rating required >5 s, the rating slide changed to the next fixation slide, which was presented for 12.5 s (Figure S1). Stimulus presentation and response collection were performed using E-Prime 2.0 Professional software (Psychology Software Tools, Sharpsburg, PA, USA).

fMRI Procedure and Training

All participants abstained from drinking alcohol and caffeine ≥24 h before fMRI scanning. Participants belonging to the smokers group were instructed not to smoke for 1 h prior to the

visit, and they were scanned within 3 h of abstinence to avoid a ceiling effect of craving (Hartwell et al., 2011; Schuh and Stitzer, 1995). Scanning was performed between 1:00 P.M. and 4:00 P.M. to minimize any circadian rhythm influence. Before scanning, the participants completed a brief training session outside the scanner. If appropriate, the participants received corrective feedback from a researcher. Self-efficacy was assessed as follows: "If you encounter a situation where certain people might be tempted to smoke, how can you be sure that you would abstain from smoking? Please answer in a range from 0 (not at all) to 100 (absolutely sure)." A single-item measure of self-efficacy has been shown to be reliable and validated (Bandura, 2006; Shadel et al., 2001).

fMRI Data Acquisition

This study was conducted using the MRI scanner and related facilities at Kokoro Research Center, Kyoto University. Data were collected using a Siemens Verio 3T scanner with a 32-channel array head coil. Functional images were obtained in a T2*-weighted gradient-echo echo-planar imaging (EPI) sequence. The image acquisition parameters were as follows: repetition time (TR) = 2500 ms; echo time (TE) = 30 ms; flip angle (FA) = 90°; field of view (FOV) = 192 mm; matrix = 64 × 64; 40 interleaved axial slices with a thickness of 3 mm and without gaps (3-mm cubic voxels). The first two volumes were not saved to allow for signal stabilization, and the subsequent 305 volumes were acquired. Each participant lay supine on a scanner bed with an MRI-compatible joystick device held in the right hand. The participants viewed visual stimuli, which were back-projected onto a screen through a built-in mirror. Structural scans were also acquired using T1-weighted three-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequences (TE = 4.38 ms; TR = 2000 ms; inversion time = 990 ms; FOV = 225 × 240 mm; 240 × 256 matrix; resolution = 0.9375 ×

0.9375 × 1.0 mm^3; 208 total axial sections without interslice gaps).

Statistical Analyses

Demographic and Behavioral Data

Student's *t*-test or Wilcoxon rank-sum test was used to compare variables between groups where appropriate. To test the effects of the strategy that focused on the self-efficacy in self-reported craving, we compared self-reported craving in the craving condition with those in the other conditions (i.e., neutral and regulation conditions) using Dunnett's test. Statistical significance was set at $p = 0.05$ (two-sided). All statistical analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA).

fMRI Data

fMRI data were analyzed using SPM8 (Wellcome Department of Imaging Neuroscience, University of London, UK; http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 2014a (MathWorks, Inc., Natick, MA, USA). The fMRI data were preprocessed as follows: the functional images were corrected for differences in slice-acquisition timing. They were also spatially realigned to the first image in the initial run to adjust for head movements and were unwarped to correct for static distortions using the Fieldmap toolbox in SPM8 (Hutton et al., 2002). Data were omitted from further analysis if absolute head motion exceeded 4 mm. A structural image (3D-MPRAGE) was coregistered to the mean of the realigned images. The coregistered structural image was normalized to a standard T1 template image as defined by the Montreal Neurological Institute (MNI). The parameters obtained from this normalization process were then applied to each of the realigned and unwarped functional images. Subsequently, all of the functional images were smoothed with an isotropic Gaussian kernel

with a full-width at half-maximum of 8 mm.

We performed first-level analysis based on a general linear model framework (Friston et al., 1994). The design matrix contained three task-related regressors (craving, regulation, neutral conditions). The rating periods and instructions were also modeled as covariates of no interest. To minimize motion-related artifacts, six realignment parameters were also included as additional regressors of no interest. Data were high-pass filtered at 128 s and corrected for serial autocorrelation. In the second-level analysis, a random-effects model was used to make inferences at the population level (Holmes, 1998) with a 2 (groups: smokers and ex-smokers) × 3 (conditions: craving, regulation, and neutral) full factorial design. Age was included as a covariate of no interest. A planned contrast was performed to evaluate the interaction between group (smoker vs. ex-smoker) and condition (regulation condition vs. craving condition). An inclusive mask was used to limit the analysis to the positively activated regions for regulation vs. craving. The main effect of group (smoker vs. ex-smoker) and the main effect of condition (regulation vs. craving) were also assessed.

To explore task-dependent functional connectivity between brain regions, we conducted a generalized form of context-dependent psychophysiological interaction (gPPI) analysis (McLaren et al., 2012). The gPPI approach improves the model fit (Friston et al., 1997; Gitelman et al., 2003) and is more powerful than the standard method (Cisler et al., 2014; McLaren et al., 2012). As seeds for the gPPI analysis, we selected brain regions involved in self-assessment, i.e., mPFC, and craving regulation, i.e., ACC, both of which showed significant interaction between group and condition according to the group analysis in our sample (see Results). The time series for each region was extracted from each participant

using the first eigenvariate of a 4-mm radius sphere centered on the aforementioned group peak coordinates. The data were high-pass filtered, whitened, and adjusted for regressors of no interest. The psychophysiological interaction terms, the task-related regressors (craving, regulation, neutral), and the time series for the seed region were entered into the first-level general linear model for gPPI analysis. Planned contrasts between regulation and craving were included in the second-level two-sample *t*-test with group (smoker vs. ex-smoker) effect. Age was added as a covariate of no interest.

All results are reported at a height threshold of $p < 0.01$, uncorrected, with a cluster threshold of k >237 voxels, equivalent to $p < 0.05$, corrected for multiple comparisons over the whole brain (i.e., family-wise error-corrected), as determined by Monte Carlo simulations using the AlphaSim program in the REST toolbox (Song et al., 2011). We identified anatomical locations of the clusters using the Automated Anatomical Labeling toolbox (Tzourio-Mazoyer et al., 2002), and a neuroanatomy atlas (Sure, 2007). Pearson's correlation coefficient was used to test associations among extracted parameter estimates or connectivity with clinical measures [i.e., Fagerström Test for Nicotine Dependence (FTND), and self-efficacy], with a statistical threshold of $p = 0.05$ (two-tailed).

RESULTS

Demographic Data and Clinical Measures

We analyzed data from 20 smokers and 22 ex-smokers. Nine smokers were excluded from the analyses due to excessive head motion ($n = 4$), loss of induced craving ($n = 3$), and anatomical abnormalities ($n = 2$). Three ex-smokers were excluded because of excessive head motion (*n*

= 1) and the exclusion criteria for ex-smokers (n = 2). The demographic data are summarized in Table 1 and Table S1. As expected, the smokers group had higher expired CO and MNWS levels compared with the ex-smokers group. The ex-smokers exhibited higher self-efficacy than the smokers group (Table 1).

Behavioral Results

There was a significant group difference in the average of the medians of self-reported craving scores: craving was induced in the smokers group, whereas little craving was induced in the ex-smokers. In the smokers group, craving was significantly higher under the craving condition compared with other conditions (Figure 1). The number of blocks after which participants failed to indicate their craving ratings within 5 seconds did not significantly differ between the groups (Table S2), and showed no significant correlation with self-efficacy in the two groups.

In addition, the strategy that focused on self-efficacy reduced self-reported craving. After scanning, the participants were asked to report what they were thinking during the craving condition and the regulation condition. We confirmed that they did not use specific strategies in the craving condition. In the craving condition, most of the smokers developed a conditioned craving response to any smoking images, reporting that they felt the urge to smoke. Nine ex-smokers showed no craving, with 3 of them feeling uncomfortable about cigarettes, indicating 0 points of craving ratings. The remaining 13 ex-smokers showed low

craving ratings (<20) temporarily for only pictures of the specific situation which evoked in them their past smoking memory. In smokers, the strategies used to resist the craving urge were divided into two subtypes: (1) recall of previous successful experiences of abstaining from smoking (*n* = 7, 35%), and (2) verbal self-persuasion (*n* = 13, 65%). A typical example of verbal self-persuasion was to repeat a phrase silently, such as "I can, I can, I can" during the regulation condition. In ex-smokers, the strategies were verbal self-persuasion (*n* = 6, 27.3%), recall of previous successful experiences of being abstinent (*n* = 7, 31.8%), acknowledging current conditions with no craving (*n* = 6, 27.3%), focusing on side effects (*n* = 2, 9.1%), and others (*n* = 1, 4.5%). The proportions of strategies employed in the regulation condition showed a significant group difference ($\chi^2(4)=11.5$, p=0.021).

fMRI Results

Regional Brain Activation

We investigated the interactions among groups (smoker vs. ex-smoker) and conditions (regulation condition vs. craving condition). There were significant interaction effects in the bilateral pregenual ACC (pgACC) and right rostral mPFC (rmPFC). The ex-smokers showed no significant activation in both rmPFC and pgACC in craving condition vs. neutral condition, corresponding to the behavioral result that they experienced no or minimal craving if any. Consequently, they also showed no significant activation in both regions in regulation condition vs. neutral condition. Due to these results, the interaction was mainly driven by the fact that the smokers group exhibited increased activation compared with ex-smokers in the regulation condition vs. craving condition (Figure 2, Figure S2, Table S3). The main effect of group (smoker vs. ex-smoker) was attributable to greater activation in the left cuneus, left

calcarine sulcus, and left occipital gyrus. The main effect of condition (regulation vs. craving) was identified in an extensive region, including the bilateral precentral and superior frontal gyri, and left mPFC (Table S4). In the following gPPI analyses, we selected right pgACC (x = 14, y = 36, z = 6) and right rmPFC (x = 32, y = 50, z = 6) as seed regions, both of which showed significant interactions between groups and conditions.

Effective Connectivity

The gPPI analysis of the contrast between regulation vs. craving condition using the right pgACC as a seed detected significantly increased functional connectivity with the right parahippocampus gyrus, right hippocampus, and right fusiform gyrus in smokers compared with ex-smokers. The smokers also exhibited task-related change (i.e., regulation vs. craving) in connectivity between the right rmPFC seed and regions of the right hippocampus, right thalamus, cerebellum vermis, bilateral cerebellum hemisphere, right lingual gyrus and right hippocampus/parahippocampal gyrus (Figure 3, Table 2).

Among the connectivities mentioned above, pgACC and rmPFC were found to be functionally connected with the right parahippocampus gyrus (x = 26, y = −26, z = −16) and right hippocampus (x = 18, y = −26, z = −8), respectively. These regions are related to memory, an important factor in cue-induced craving (Volkow et al., 2003; White, 1996) and self-efficacy (Bandura, 1977; Bandura, 1996). Therefore, we focused on the two connectivities between pgACC and parahippocampus gyrus (ACC-parahippocampus), and between rmPFC and hippocampus (mPFC-hippocampus). In smokers, the magnitude of ACC-parahippocampus connectivity was positively correlated with FTND (r = 0.47, p = 0.036), but not with the self-efficacy score (r = 0.28, p = 0.22) (Figure 3). The magnitude of mPFC-

hippocampus connectivity was positively correlated with the self-efficacy score (r = 0.55, p = 0.012) but not with FTND (r = 0.29, p = 0.22). The VAS reduction from craving condition to regulation condition did not correlate with the magnitude of mPFC-hippocampus connectivity (r = 0.24, p = 0.31) and of ACC-parahippocampus connectivity (r = 0.19, p = 0.43).

To assess the differences in functional connectivity between the sub-strategies of self-efficacy strategy, we divided the smokers into two groups according to their strategies, i.e., "memory group" (MG: n = 7), who recalled past success; and "verbal group" (VG: n = 13), who employed verbal self-persuasion. In MG, the mPFC-hippocampus connectivity in regulation vs. craving was 0.69 ± 0.38, which was significantly higher than that in VG (0.042 ± 0.402) (t = 3.24, p = 0.005). The degree of ACC-parahippocampus gyrus connectivity in MG (0.670 ± 0.572) tended to be stronger than that in VG (0.148 ± 0.609) (t = 1.83, p = 0.078). These groups did not differ in terms of their demographic characteristics, smoking history, abstinence period, nicotine dependency, and craving reduction in VAS score.

DISCUSSION

A strategy focused on self-efficacy significantly reduced self-reported craving in smokers. The smokers group exhibited increased activation of two brain regions —rmPFC and pgACC — compared with the ex-smokers group when using this strategy. Furthermore, connectivity analyses revealed that mPFC-hippocampus connectivity and ACC-parahippocampus connectivity increased during regulation of craving. In the craving condition, most of the smokers felt a craving for any smoking images. On the other hand, ex-smokers experienced no craving or only temporary slight craving during the condition. In line with this behavioral result, ex-smokers showed no significant activation in rmPFC and pgACC, implying that ex-

smokers needed virtually no effort to resist the craving. Thus, increased brain activation and connectivity during regulation condition in smokers may reflect the cognitive effort to regulate craving.

The cognitive effort here should include a more general process such as attentional control or emotional control required for regulating craving in addition to the central process of self-efficacy strategy. Although general and central processes are not mutually exclusive, we discuss each process in consideration of the contrasting brain regions (pgACC and mPFC, respectively). According to connectivity analysis, these two regions were not functionally connected with each other during the task, and each region seems to work independently in the process of regulating craving.

Both pgACC and rmPFC are implicated in negative emotional processing (Etkin et al., 2011). Specifically, rmPFC is involved in appraisal of negative emotion, whereas the pgACC plays a general role in regulating negative emotion (Etkin et al., 2011), which is also implicated in craving regulation (Peters et al., 2009). In fact, previous study reported that this region was involved in resisiting craving in tobacco-dependent smokers (Brody et al., 2007). We found that pgACC was more strongly connected with the parahippocampus gyrus in smokers during the regulation condition compared to the craving condition. In addition, this connectivity was positively correlated with nicotine dependency. Although the hippocampal region has multiple functions of memory in general as well as other functions considering its connection with pgACC in the context of regulation of emotion and craving, this region might be

involved in contextual processing, particularly for emotional memory (Maren et al., 2013). The hippocampus/parahippocampus gyrus has been reported to be activated by cue-induced craving (Grant et al., 1996; Volkow et al., 2003). Cue-induced craving is one of the contextual conditioned reactions (Selden et al., 1991), which require the functioning of the parahippocampus gyrus (Rudy, 2009) and the hippocampus (McClernon et al., 2016; Robbins et al., 2008) as a system. Considering the function of pgACC in inhibiting negative emotion as mentioned above (Etkin et al., 2011), increased pgACC-parahippocampus connectivity in smokers may reflect the effort to inhibit negative emotion evoked by cue-induced craving, a contextual conditioned reaction, in the group. This notion may be supported by a previous study of cognitive regulation using mindfulness in an opposite manner (Westbrook et al., 2013). Mindfulness does not require effort to regulate craving, but instead it accepts craving for what it is. The study that used mindfulness as a strategy to overcome craving showed that activity in pgACC and its connectivity with a craving-related region were decreased during the task (Westbrook, et.al, 2013). These results and our findings suggest that an intention to regulate craving induces activity in pgACC and modulates its connectivity with the parahippocampus gyrus.

In contrast, as described above, rmPFC is involved in (re)appraisal of negative emotion.

Reappraisal involves both the initial emotional appraisal process as well as an additional positive appraisal that competes with the initial negative emotional appraisal (Etkin et al., 2011). Ability to implement cognitive reappraisal when one wishes to regulate one's emotions is an important factor of self-efficacy (Goldin et al., 2009). Besides the role in emotional processing, rmPFC is crucial for self-assessment (D'Argembeau et al., 2007; Ochsner et al., 2005), one of the components of self-efficacy. In addition, connectivity between mPFC and hippocampus during the regulation condition in smokers was positively correlated with self-efficacy score. Thus, mPFC activation and mPFC-hippocampus connection appear to partly reflect the central process of self-efficacy starategy. At the same time, this connectivity was significantly stronger in individuals who used recall of successful experiences to abstain from smoking (i.e., successful memory), compared with those who used verbal self-persuasion in the regulation condition. Again, although the hippocampus has mutiple functions in memory and other cognitive functions, it would be natural to assume that the mPFC-hippocampus connection might play a role in self-related memory because both mPFC and hippocampus are important for autobiographical memory (Buckner, 2010). The mPFC-hippocampus connectivity may reflect self-referential processing based on autobiographical memory of successfully overcoming craving. Importantly, the effort to recall positive successful memory in the face of primarily negative situation (craving-inducing situation) is neither more nor less

than cognitive reappraisal.

A major strength of our study was that we included the data of ex-smokers. The fact that ex-smokers experienced less craving and required less effort to regulate craving implies that the comparison between smokers and ex-smokers enabled us to detect the neural basis of the regulation of craving in smokers. Thus, ex-smokers serve as a good control group. This study also has several limitations. First, the sample was small and consisted of males only. Previous studies reported that male smokers have higher self-efficacy to remain abstinent in high-risk situations (Etter et al., 2002; Pelissier and Jones, 2006) and less subjective cue-induced craving (Field and Duka, 2004) compared with females. Furthermore, gender difference has been shown in neural reactions during exposure to smoking-related cues (Potenza et al., 2012; Wetherill et al., 2013). Thus, caution should be exercised in generalizing our present findings to female smokers. Third, self-efficacy strategy has consisted of several components and has been built on integrated information from multiple sources. Thus, it may be difficult to distinguish self-efficacy-related processes from processes that are shared with other psychological tasks. Fourth, gPPI analysis does not address causality. Thus, the causal relationships between activation of the hippocampus/parahippocampus gyrus and pgACC and rmPFC were not determined. Finally, although we possessed a hypothesis based on previous literatures, brain regions such as ACC and mPFC have multiple functions. At the same time, our task cannot extract a single cognitive component from the whole complex process of regulating craving. Thus, interpretation of our results regarding brain function should be approached with caution.

In conclusion, a strategy focused on self-efficacy was effective in reducing self-reported craving for cigarettes in smokers. Furthermore, our results suggest that rmPFC and mPFC-hippocampus connectivity play roles in enhancing cognitive reappraisal, whereas pgACC and ACC-parahippocampus connectivity play roles in suppressing craving. Our findings may help to understand the cognitive and neurobiological mechanisms related to effective control of craving for smoking.

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Table 1. Demographic data for clinical measures

		Smoker	**Ex-smoker**	**Statistics**
		N = 20	**N = 22**	
		Mean (SD)	**Mean (SD)**	***p*-value**
Age	(years)	38.7 (10.0)	43.6 (7.8)	0.087[b]
BMI	(kg/m^2)	23.0 (3.3)	24.3 (5.6)	0.387[b]
SES 1/2/3/4 (N)		0/6/11/3	4 /6/11/1	0.120[c]
Age at starting smoking	(years)	18.9 (1.8)	18.6 (2.7)	0.720[b]
Cigarettes per day[a]		18.9 (6.9)	24.9 (15.0)	0.106[b]
Years of smoking	(years)	19.5 (10.0)	22.8 (8.7)	0.279[b]
Abstinent period	(months)	-	42.9 (33.0)	-
FTND[a]		4.6 (2.0)	5.8 (2.6)	0.075[b]
Alcohol	(unit/day)	1.7 (2.0)	0.9 (1.7)	0.189[b]
Exhaled CO level	(ppm/l)	21.5 (13.0)	3.0 (1.0)	< 0.001[c]
Self-efficacy		57.5 (4.6)	94.6 (6.5)	< 0.001[b]
MNWS		9.2 (7.0)	4.4 (3.6)	0.010[b]

[a]Ex-smokers' data were retrospective, [b]Student's *t*-test, [c]Wilcoxon rank-sum test.

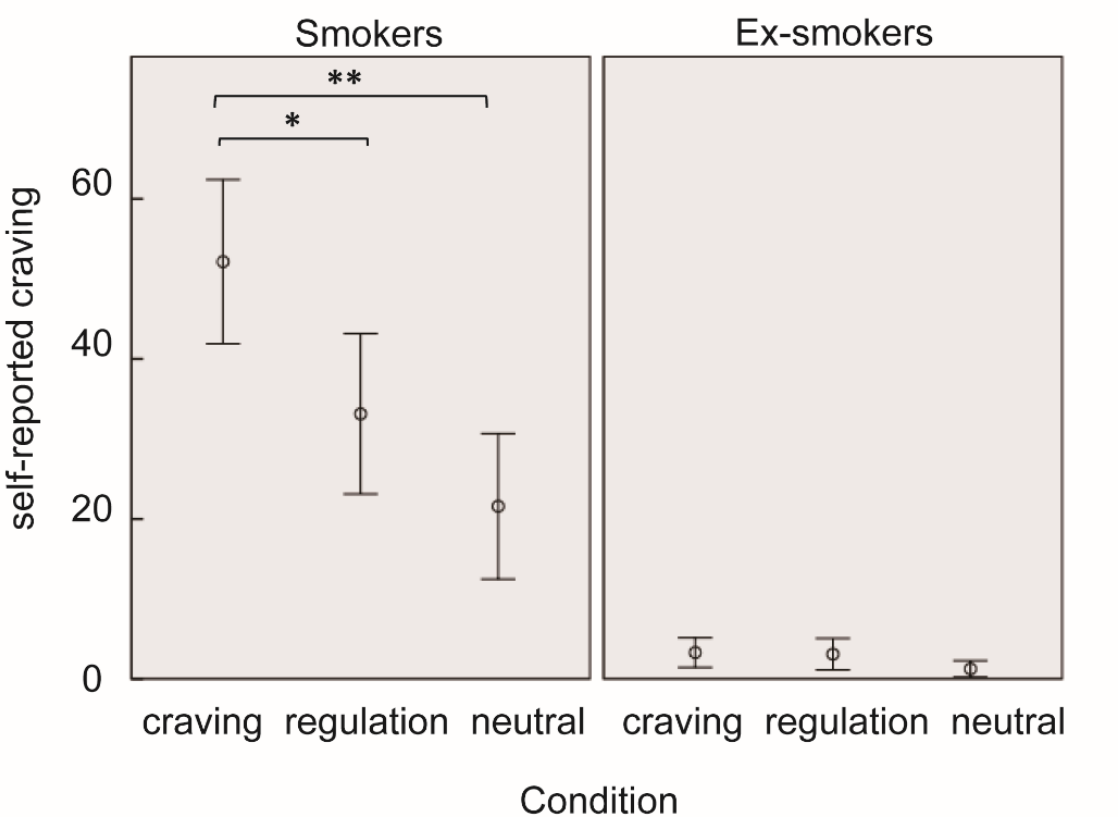
SES: socioeconomic status (1 = major business and professional, 2 = medium business and technical, 3 = skilled craftsmen, clerical, sales workers, 4 = machine operators, semi-skilled workers), CO: carbon monoxide, FTND: Fagerström Test for Nicotine Dependence, MNWS: Minnesota Nicotine Withdrawal Scale

Table 2. Brain regions showing significant connectivity with seeds (rmPFC and pgACC)

Brain regions	Cluster (voxel)	t	MNI coordinates (mm) x	y	z
Seed rmPFC					
R Hippocampus	264	3.17	18	−26	−8
Cerebellum vermis	408	4.4	−2	−42	−16
Seed pgACC					
R parahippocampal gyrus	239	3.43	26	−26	−16

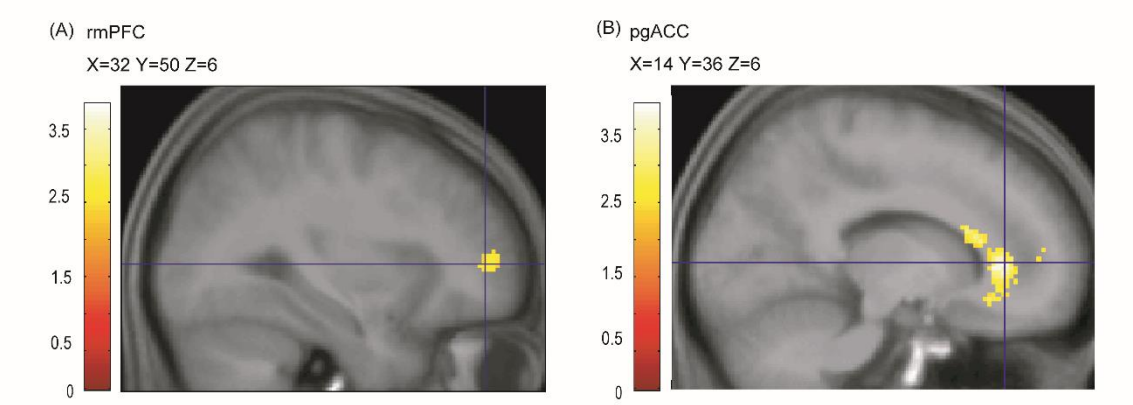
MNI coordinates and *t*-values are provided for peak voxels in the clusters; R = right, rmPFC = rostral medial prefrontal cortex, pgACC = pregenual anterior cingulate cortex

Figure 1. Self-reported craving in smokers and ex-smokers



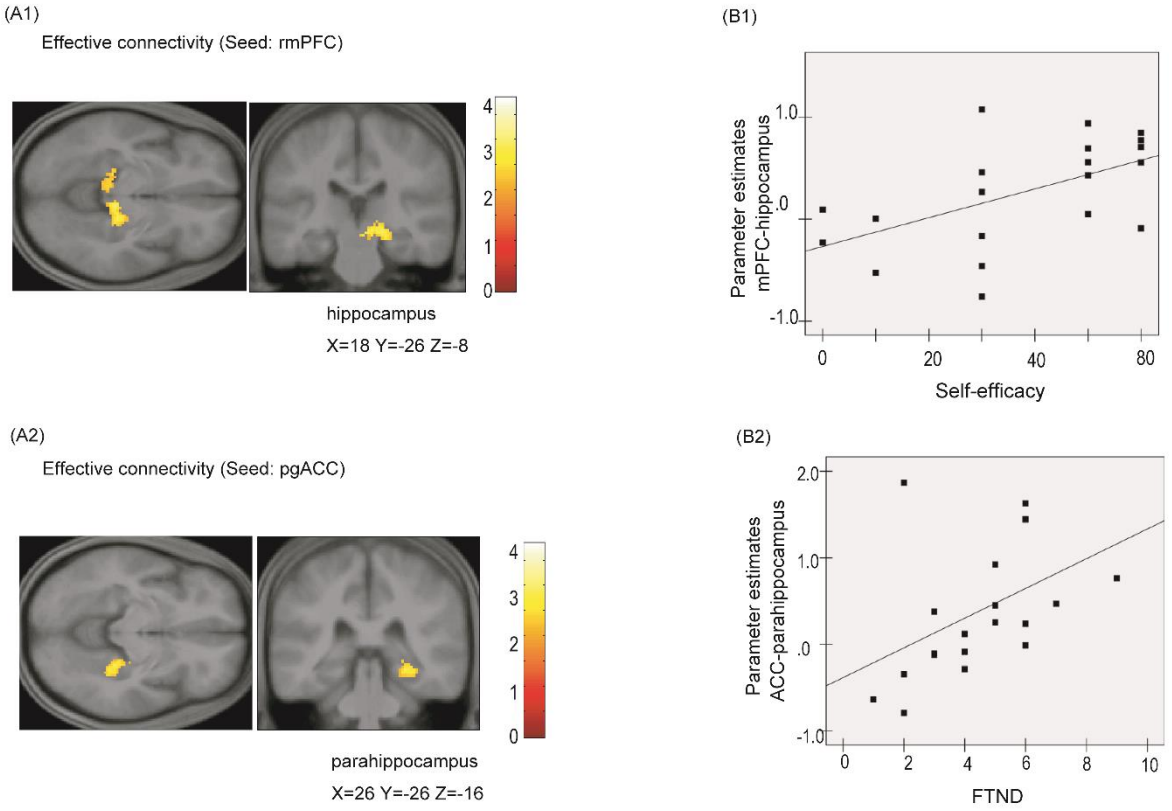
While the ex-smokers group exhibited little craving under each condition, the smokers group showed significantly higher craving rates in the craving condition compared with that in the regulation and neutral conditions (*p = 0.015 and **p < 0.0001, respectively). Error bars denote the 95% confidence interval (CI).

Figure 2. Brain regions showing significant group x condition interactions



Statistical parametric map of the interactions between group (smoker>ex-smoker) and condition (regulation>craving). rmPFC = rostral medial frontal cortex, pgACC = pregenual anterior cingulate cortex

Figure 3. Effective connectivity and correlations between effective connectivity and behavior



(A) Brain regions showing higher effective connectivity of cognitive regulation (regulation vs. craving) in smokers compared with ex-smokers [seeds: (A1) rmPFC and (A2) pgACC]. (B) Scatter graphs showing the correlations between effective connectivity and behavioral measures; (B1) mPFC-hippocampus connectivity and pre-scan self-efficacy score (r = 0.55, p = 0.012), and (B2) ACC-parahippocampus connectivity and FTND (r = 0.47, p = 0.036). rmPFC = rostral medial prefrontal cortex, pgACC = pregenual anterior cingulate cortex