Progress in Neuro-Psychopharmacology & Biological Psychiatry 38 (2012) 285–293

Contents lists available at SciVerse ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Individual differences in smoking-related cue reactivity in smokers: An eye-tracking and fMRI study

O-Seok Kang [a,1], Dong-Seon Chang [a,1], Geon-Ho Jahng [b], Song-Yi Kim [a], Hackjin Kim [c], Jong-Woo Kim [d], Sun-Yong Chung [d], Seung-In Yang [a], Hi-Joon Park [a], Hyejung Lee [a], Younbyoung Chae [a,c,*]

[a] *Acupuncture and Meridian Science Research Center, Kyung Hee University, Seoul, Republic of Korea*
[b] *Dept. of Radiology, University Hospital-Gangdong, School of Medicine, Kyung Hee University, Seoul, Republic of Korea*
[c] *Dept. of Brain Cognitive Engineering, Korea University, Seoul, Republic of Korea*
[d] *Dept. of Neuropsychiatry, College of Oriental Medicine, Kyung Hee University, Seoul, Republic of Korea*

ARTICLE INFO

Article history:
Received 31 December 2011
Received in revised form 15 April 2012
Accepted 15 April 2012
Available online 21 April 2012

Keywords:
Addiction
Attentional bias
Cue reactivity
Eye movement
fMRI
Smoking

ABSTRACT

Measures of cue reactivity provide a means of studying and understanding addictive behavior. We wanted to examine the relationship between different cue reactivity measures, such as attentional bias and subjective craving, and functional brain responses toward smoking-related cues in smokers. We used eye-tracking measurements, a questionnaire for smoking urges-brief and functional magnetic resonance imaging to assess the responses to smoking-related and neutral visual cues from 25 male smokers after 36 h of smoking abstinence. Regression analyses were conducted to determine the correlation between cue-evoked brain responses and the attentional bias to smoking-related cues. The eye gaze dwell time percentage was longer in response to smoking-related cues than neutral cues, indicating significant differences in attentional bias towards smoking-related cues. The attentional bias to smoking-related cues correlated with subjective craving ratings ($r = 0.660$, $p < 0.001$). The dorsolateral prefrontal cortex, the putamen, the posterior cingulate cortex and the primary motor cortex were associated with the attentional bias to smoking-related cues, whereas the orbitofrontal cortex, the insula and the superior temporal gyrus were associated with smoking-related cue-induced craving and smoking urges. These results suggest that attentional mechanisms in combination with motivational and reward-related mechanisms play a role in smoking-related cue reactivity. We confirmed a positive correlation between different smoking-related cue reactivities, such as attentional bias and subjective craving, and functional brain responses in various individuals. Further studies in this field might contribute to a better individualized understanding of addictive behavior.

1. Introduction

Drug addiction is characterized by the motivational disturbances of compulsive drug taking and intense drug craving (Koob and Le Moal, 2001; Self, 1998). The cue-reactivity paradigm has been suggested as providing a means of measuring and extricating the concept of craving. Drug addiction can be studied experimentally using this paradigm; after exposure to a drug-related cue, a variety of responses that can be behavioral (e.g., drug-seeking or consumption), physiological (e.g., sweating or salivation), or symbolic-expressive (e.g., craving or anxiety), can be observed and measured, although establishing a clear distinction between these categories is sometimes difficult (Drummond, 2000). The measurement of eye gaze towards drug-related cues has recently emerged as a useful method to study drug-seeking behavior (Mogg et al., 2005). Previously, typical physiological responses were measured by changes in activity of the autonomic nervous system, such as heart rate variability or pupil size changes (Chae et al., 2008; Niaura et al., 1989). More recently, neuroimaging methods, such as functional magnetic resonance imaging (fMRI), have emerged as powerful tools to study the neurophysiological changes in brain activity following cue exposure (David et al., 2005; Due et al., 2002; Janes et al., 2010; Luijten et al., 2010). Symbolic-expressive responses have typically been measured using questionnaires, and a number of research studies on craving have been conceptualized and performed using self-report measures (Sayette et al., 2000).

Attentional bias, one of the central behavioral features of cue reactivity, has been suggested to be related to enhanced smoking urges and

Abbreviations: ACC, anterior cingulate gyrus; BOLD, blood oxygen level-dependent; CO, carbon monoxide; DLPFC, dorsolateral prefrontal cortex; FTND, Fagerstrom Test for Nicotine Dependence; fMRI, functional magnetic resonance imaging; IAPS, International Affective Picture System; OFC, orbitofrontal cortex; PCC, posterior cingulate gyrus; QSU-Brief, Questionnaire on Smoking Urges-Brief; MI, primary motor cortex; SMA, supplementary motor area; STG, superior temporal gyrus.

* Corresponding author at: Acupuncture & Meridian Science Research Center, Kyung Hee University, 1 Hoegi-dong, Dongdaemun-gu, Seoul, 130-701, Republic of Korea. Tel.: +82 2 961 2208; fax: +82 2 963 2175.
E-mail address: ybchae@khu.ac.kr (Y. Chae).
[1] Equally contributed to this study as co-first authors.

0278-5846/$ – see front matter. Crown Copyright © 2012 Published by Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2012.04.013

craving (Field and Cox, 2008; Hogarth et al., 2008; Robbins and Ehrman, 2004). Studies of attentional bias toward smoking-related cues have used selective attention tasks, such as the Emotional Stroop Task (Mogg and Bradley, 2002; Waters et al., 2003b) or the Visual Probe Task (Bradley et al., 2004; Ehrman et al., 2002). Depending on the task, different underlying attentional processes can be measured; the Emotional Stroop Task measures non-automatic attentional processes (higher-level executive/cognitive control), whereas the Visual Probe Task is more able to capture fast and automatic attentional processes (basic low-level/habit-strength behavior), although both levels of attentional processing are known to act similarly in nicotine addiction (Chiamulera, 2005; Kassel, 1997). Eye-tracking systems can be used to record the eye movements of subjects assessing shifts in visual-selective attention, and either the initial shift in attention (first fixation) or maintained attention (longer gaze time = dwell time percentage) serves as markers of attentional bias. Studies have shown that maintained attention is best measured for longer durations (>2000 ms) when using the Visual Probe task and that it plays a greater role in cue-reactivity to smoking-related cues (Mogg et al., 2003).

The neural responses to smoking-related cues in smokers have been investigated as changes in blood oxygen level-dependent (BOLD) signals in the brain using fMRI (Brody et al., 2007; Due et al., 2002; McBride et al., 2006; McClernon et al., 2009). Brain circuits involved in reward and motivation, as well as in learning, memory and control, are implicated in the processes of smoking addiction (Breiter and Rosen, 1999; David et al., 2005). It has been reported that cue-induced craving and brain activation responses to smoking cues are highly correlated in the components of the mesolimbic reward system and in memory circuits, whereas the severity of nicotine dependence is correlated with cue-induced activation of the circuits linked to visuo-spatial attention and motor function (Smolka et al., 2006; Yalachkov et al., 2009, 2010). The relationship between attentional bias and brain reactivity to smoking-related cues has not been sufficiently elucidated to date. Subjective craving and the urge to smoke have been suggested to be closely related to attentional bias for smoking-related cues (Mogg et al., 2005; Waters and Feyerabend, 2000). Correlations between subjective craving and smoking cue-induced changes in brain metabolism have also been reported in many studies with a large degree of agreement across studies (Brody et al., 2002; McClernon et al., 2005). Recent studies have also demonstrated the neural correlation between drug-related attentional bias and brain activation (Janes et al., 2010; Luijten et al., 2010). However, it would also be important to compare the different kinds of cue reactivity to see whether individual differences in these disparate types of cue responses are correlated.

In the current study, we aimed to look for a relationship between different measures of cue-reactivity; attentional bias was measured in smokers exposed to smoking-related cues through eye movements (behavioral cue reactivity), the functional activation of attention-, reward- and motivation-related brain areas (physiological cue reactivity) and subjective measures for craving (symbolic-expressive cue reactivity). Moreover, we looked for brain regions related to individual differences in brain activation to smoking-related cues.

In this study, we wanted to examine the following questions in smoking-addicted individuals: (i) whether the level of subjective craving was associated with attentional bias to smoking-related cues; (ii) whether individual differences in attentional bias score co-varied with functional brain activity responses to smoking-related cues; and (iii) whether individual differences in smoking urge and subjective craving score co-varied with functional brain activity responses to smoking-related cues.

2. Methods

2.1. Participants

Twenty-five right-handed male smokers, free of any medication, were recruited for this study if they smoked at least ten cigarettes per day for over three years. All participants had normal visual acuity, and those with psychiatric or neurological disorders were excluded. All psychiatric disorders were identified by a psychiatrist using the structured diagnostic tool, Diagnostic and Statistical Manual of Mental Disorder IV. The participants were originally recruited to receive acupuncture (or placebo) treatment for smoking cessation; however, all of the tests described in the current paper were carried out in a separate session before receiving any kind of acupuncture (or placebo) treatments (data regarding the efficacy of acupuncture for smoking cessation is in preparation for a separate manuscript). The subjects agreed to abstain from smoking for two days prior to the fMRI scanning session, and all sessions took place after approximately 36 h of smoking deprivation. To verify smoking abstention, a carbon monoxide (CO) monitor (The Bedfont Instrument, Kent, UK) was used, and a CO value of less than 5 ppm indicated that the subjects had been compliant with the abstinence requirement. All participants gave informed consent for the study. This investigation was approved by the Institutional Review Board of University Hospital-Gangdong, Kyung Hee University, Seoul, Republic of Korea.

2.2. Smoking-related and neutral visual cues

The smoking-related and neutral visual cues were pictorial stimuli that were slightly modified from those we had used in our previous study (Chae et al., 2010). The smoking-related visual cues consisted of 15 color photographs of smoking-related scenes (e.g., a man holding a cigarette to his mouth). Each of the smoking-related visual cues was paired with neutral visual cues (e.g., a man holding a spoon to his mouth) that were matched as closely as possible for the visual characteristics (e.g., color, brightness, background scene). To check whether and to what degree the smoking-related visual cues induced a reaction in smokers, we obtained valence ratings to all smoking-related and neutral cues in a previous study. Whether the smoking-related pictures appeared on the left or the right side of the screen was counter-balanced. Five neutral picture pairs unrelated to smoking were taken from the International Affective Picture System (IAPS) and used in filler trials. The pictures were digitized and converted to an indexed 256-color palette. The pictures were approximately 14 cm wide and 10 cm high, and the distance between the inner edges of each picture in each pair was approximately 4 cm, as shown in Fig. 1A. The same smoking-related and neutral visual cues were used for the eye-tracking and the fMRI scanning sessions.

2.3. Eye tracking task design

The tasks were presented in a dimly lit, sound-proofed room using a 1700-MHz PC with a 17 in. LCD-TFT monitor. Participants' eye movements were recorded during the experiment with a computerized eye-tracking system (iView X^{TM} RED, SensoMotoric Instruments, Germany). In the eye-tracking task, each trial started with fixation for 2000 ms on a central cross, which was replaced on the display with a pair of pictures for 6000 ms. The stimulus exposure time was chosen according to previous studies, which showed that longer exposure duration was better to measure maintenance of attention compared to initial attention and resulted in more differences in attentional bias between smokers and nonsmokers (Bradley et al., 2004; Mogg et al., 2003). Participants were seated at a desk at a constant distance of 1 m from the monitor and were instructed to look at the fixation cross at the start of each trial and to be motionless and refrain from moving their heads during the task.

2.4. Preparation of eye movement data

The eye-tracking data were analyzed using the Eye Tracking Data Analysis Program (BeGaze, SensoMotoric Instruments, Germany). The direction of gaze was measured in degrees once every 17 ms.