An Increase in Tobacco Craving Is Associated with Enhanced Medial Prefrontal Cortex Network Coupling

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Published Version</td>
<td>doi:10.1371/journal.pone.0088228</td>
</tr>
<tr>
<td>Citable link</td>
<td><a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:11879940">http://nrs.harvard.edu/urn-3:HUL.InstRepos:11879940</a></td>
</tr>
<tr>
<td>Terms of Use</td>
<td>This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA</a></td>
</tr>
</tbody>
</table>
An Increase in Tobacco Craving Is Associated with Enhanced Medial Prefrontal Cortex Network Coupling

Amy C. Janes*, Stacey Farmer, Blaise deB. Frederick, Lisa D. Nickerson, Scott E. Lukas

McLean Imaging Center, McLean Hospital, Harvard Medical School, Belmont, Massachusetts, United States of America

Introduction

Craving, or the strong desire to use an abused substance, is a key component of drug addiction, and is a motivator for drug use [1,2]. To understand craving, research has focused on identifying the neurobiological substrates underlying the desire to use drugs. However, craving is linked with a number of brain regions, such as those involved in primary drug reward, habitual drug use, memory, and reward based-decision making [3–8]. Thus, it is hypothesized that a distributed brain network mediates craving instead of a single localized region [9]. An increase in craving may, therefore, involve enhanced brain region interactions that facilitate integration of information across these disparate brain areas.

The relationship between craving and brain-network interactions can be evaluated using functional magnetic resonance imaging (fMRI) data collected at rest. While previous task-related fMRI research has identified discrete brain regions associated with craving [6,8], resting-state fMRI allows for the evaluation of brain function at a more distributed network level. During rest, brain regions with highly correlated fluctuations in blood oxygen level dependent (BOLD) signals are defined as functional networks [10], called resting state networks (RSNs), which are thought to reflect intrinsic functional brain organization [11,12]. Subsequent research has revealed that RSNs are associated with known brain systems related to cognition, perception, and reward [13,14]. To evaluate associations between craving and network-level brain changes, we collected resting-state fMRI and subjective craving data in nicotine-dependent smokers at two time points approximately one hour apart. Over this one-hour time period, participants reported a significant rise in craving as measured by the brief questionnaire of smoking urges (QSU) [15].

We focused on the orbital and medial prefrontal cortex (OMPFC) network, which is a previously defined RSN [13,16] comprised of anatomically interconnected brain regions [17] involved in the mesocorticolimbic reward circuit. Specifically, the OMPFC network contains the medial and orbital prefrontal cortex (mPFC, OFC), and the subgenual anterior cingulate cortex (sgACC) extending into the ventral striatum. We focused on this network as these prefrontal and striatal regions are implicated in craving [4,7,18] drug reinforcement [19,20], and reward processing [21]. Additionally, the OFC is thought to be a multimodal integration area leading to hedonic experience [22]. In addition to the direct link between OMPFC brain regions and craving, this network may act as a hub [23] where information is integrated to facilitate the subjective experience of craving. To confirm the idea that a distributed brain network is associated with craving, we hypothesize that interactions between the OMPFC network and other craving-related brain regions will increase along with a rise in the subjective experience of craving.

Methods

Participants

Seventeen nicotine-dependent smokers (8 men/9 women) were studied: 25.4±4.6 (mean ± standard deviation) years old with 15.3±2.1 years of education and 6.7±4.7 pack-years of smoking...
use (pack years = number of packs of cigarettes smoked/day x years as a smoker). Participants had an average Fagerstrom test for nicotine dependence (FTND) [24] score of 6.3±1.0, which confirmed moderate to severe nicotine dependence. Participants also reported smoking ≥10 cigarettes/day over the past 6 months. The Structured Clinical Interview for DSM-IV (SCID) was used to assess all participants for current nicotine dependence and to exclude those with a lifetime diagnosis of the following conditions: organic mental disorder, bipolar or unipolar depression, or schizophrenia spectrum disorder. Participants also were excluded for pregnancy, current psychotropic drug use or recent alcohol use (Alco-Sensor FST, Intoximeters, Inc.). No participants consumed any alcohol prior to the study as indicated by a blood alcohol level of 0. Additionally, no subjects met criteria for alcohol abuse or dependence. Recruitment was conducted using online advertisements and fliers posted in the Boston area. All participants gave written informed consent prior to participating in the study and the institutional review board at McLean Hospital approved this study and consent procedure.

Functional Neuroimaging

All participants smoked one of their own cigarettes immediately following signing the informed consent to standardize the time since a cigarette was last smoked. MRI scanning began approximately 1.5 h after smoking this cigarette. Scans were acquired on a Siemens Trio 3 Tesla scanner (Erlangen, Germany) with a 32-channel head coil. Multiecho multiplanar rapidly acquired gradient-echo (ME-MPRAGE) structural images were acquired with the following parameters (TR = 2.1 s, TE 3.3 ms, slices = 128, matrix = 256 x 256, flip angle = 7°, resolution = 1.0 mm x 1.0 mm x 1.33 mm), and gradient echo echo-planar images were acquired using the following parameters (TR = 2.5 s, TE = 30 ms, flip angle = 90°, slices = 42, voxel size = 3.5 mm isotropic). Slices were acquired aligned to the anterior and posterior commissure and the phase encode direction was set to 0.5 mm isotropic. After the individual subject's dataset, to identify voxels correlated with the change in craving and CO, nor was the difference in craving and CO associated with age, pack-year, or FTND score.

Craving, measured by the QSU, significantly increased just prior to the first resting state scan and just after the second resting state scan, craving was measured by the brief 10-item Questionnaire of Smoking urges [15]. Expired carbon monoxide (CO; Micro Smokerlyzer II, Bedfont Scientific Instruments) was also measured at these two time periods. Significant differences in craving and CO at these two time periods were assessed using a paired t-test. Changes in craving and CO were calculated by subtracting the second (post-scan) minus the first (pre-scan) measurements. Changes in craving and CO were correlated with the RSN difference maps using non-parametric permutation testing using 5,000 permutations (FSL Randomize) [30]. Multiple comparisons were corrected to p<0.05 using cluster-based thresholding where the cluster-forming threshold was Z=2.3 [31].

Results

Craving and Enhanced Brain Network Coupling

To calculate subject specific time courses and spatial maps, we used a dual regression approach [27–29]. In the first stage of dual regression, the full set of group ICs, which include all RSNs and artifact components, are used in a multiple spatial regression against each individual subject’s dataset to estimate the average time course of voxels in each RSN. By including all of the ICs in the multiple regression, any voxel with contributions from multiple signal sources (for example, from coupling with an RSN and from motion effects) will have these effects partialled out into their separate contributions by the multiple regression prior to the averaging. The subject-specific time courses were normalized to unit variance and then used in a second multiple regression against the individual subject’s dataset, to identify voxels correlated with each of the RSN time courses, thus identifying the spatial map of each RSN unique to the subject. To evaluate a change in functional connectivity between the two resting state acquisitions, difference maps were calculated by subtracting the individual subject specific spatial maps for the second minus the first resting state session.

Resting State Associations with Craving and Carbon Monoxide

Just prior to the first resting state scan and just after the second resting state scan, craving was measured by the brief 10-item Questionnaire of Smoking urges [15]. Expired carbon monoxide (CO; Micro Smokerlyzer II, Bedfont Scientific Instruments) was also measured at these two time periods. Significant differences in craving and CO at these two time periods were assessed using a paired t-test. Changes in craving and CO were calculated by subtracting the second (post-scan) minus the first (pre-scan) measurements. Changes in craving and CO were correlated with the RSN difference maps using non-parametric permutation testing using 5,000 permutations (FSL Randomize) [30]. Multiple comparisons were corrected to p<0.05 using cluster-based thresholding where the cluster-forming threshold was Z=2.3 [31].

Identified resting state network

The OMPFC network common to all subjects included the ventromedial PFC (Broadmann area (BA) 10), orbitofrontal cortex (OFC; BA 11), subgenual ACC (BA 24, 32), and the ventral striatum/nucleus accumbens extending into the adjacent caudate.
Carbon Monoxide associations with RSNs

No associations were found between CO and any of the RSN measurements.

Discussion

The current results identify that a relationship exists between increased subjective craving and enhanced coupling between the OMPFC network and several other brain regions. This association was noted only when evaluating the change in craving as no interaction was found between craving and RSN measures at either time point one or two alone. This suggests that stable levels of craving are not related to network functional connectivity strength, but experiencing a rise in craving is accompanied by greater OMPFC network coupling. While others have evaluated the relationship between nicotine withdrawal symptoms and the default mode and executive control networks [28], this is the first focused evaluation of craving on reward-related brain networks. As we found no correlation between the decrease in expired CO and OMPFC network coupling, the relationship between craving...
and changes in connectivity cannot be attributed to physiological changes due to a drop in CO.

There is a strong link between the OMPFC network and craving as regions within this network, which include the vmPFC, OFC, sgACC, and striatum, activate during craving [4,32]. Several, but not all studies also report deactivation of these regions during the regulation of craving [4,32–35]. Supporting the idea that OMPFC regions act as a craving-related functional unit, Hanlon and colleagues [4] showed that this entire cluster of brain regions activates during tobacco craving. More broadly the OMPFC network may be involved in reward evaluation during the experience of craving, as OMPFC network regions are active during both reward anticipation and reward delivery [36–40].

In the present study, increased subjective craving paralleled enhanced coupling between the OMPFC network and brain regions that typically activate when drug users are exposed to drug-associated cues; including dorsal regions of the mPFC [41], the hippocampus [42], visual areas [41,43], sensory motor regions [44], the striatum [7,43], and cerebellum [46]. This co-activation of prefrontal and other cortical, limbic, striatal, and visceromotor areas led London and colleagues [18] to speculate that there is an “interplay of related networks” during drug-cue exposure that may correspond with craving. Our findings confirm that a rise in subjective craving is correlated with enhanced coupling between brain regions associated with craving, which are also anatomically connected with the OMPFC [17]. These rich interconnections with OMPFC brain regions are thought to form a sensory-visceromotor link to guide reward-related behavior and give rise to hedonic experience [17,22]. Thus, it is possible that the integration of information between these regions may play a role in the experience of craving as well as guiding smoking behavior.

In the context of the current study, we are unable to directly determine whether there is a link between increased brain network coupling and behavior. However, as craving intensity peaks prior to relapse [47], it is tempting to speculate that that the enhanced coupling between brain regions associated with increased craving facilitates smoking-related behavior. Increased craving-related coupling between the OMPFC network and regions such as the supplementary motor area (SMA) supports the notion that the observed network-interactions may have an impact on behavior. Not only does the SMA activate to smoking-related cues [44], but SMA neurons fire prior to hand movements, which is thought to facilitate psychomotor responses to an object [48]. Thus, the interaction between these brain regions implicated in craving and behavior may actually be involved in the process of “preparing to smoke”. Alternatively, as smokers were in the scanner and unable to smoke ad libitum, when they had the immediate desire, the involvement of brain regions such as the SMA may regulate smoking behavior as the SMA also is implicated in the inhibition of action [49].

Future directions not only include linking network changes with behavior, but also defining the neurotransmitter systems mediating brain network connectivity. For instance, greater midbrain dopamine D3 receptor availability is positively correlated with enhanced coupling between the OMPFC network and brain structures such as the striatum and OFC [50]. In addition, D3 receptors play a strong role in nicotine-seeking and are a promising target for nicotine cessation treatment [51–53]. These studies suggest that future research should focus on the role of D3 receptors in craving-related OMPFC network coupling. Given that D3 receptors influence other addictive disorders [54], these future studies should be expanded to include craving-related network changes for nicotine and other abused substances. While we found no relationship between craving and factors such as age and level of nicotine dependence, these factors should also be studied more directly as our work focused specifically on relatively young and heavily nicotine dependent smokers. Finally, while we speculate that OMPFC brain regions may act as an integrative hub [23], future studies involving alternative connectivity methods should focus on identifying the directionality of information flow between craving-related brain structures.

Our results confirm that increased tobacco craving is associated with enhanced interactions between reward- and craving-related brain regions. This rise in craving over time was not related to baseline measures of smoking history, nor was the change in brain regions. This rise in craving over time was not related to baseline measures of smoking history, nor was the change in brain regions. Therefore, changes in OMPFC coupling are specifically related to enhanced subjective craving. The relationship between changes in craving and RSN connectivity indicate that brain network interactions are associated with changes in subjective state.

Author Contributions

Conceived and designed the experiments: ACJ SEL. Performed the experiments: ACJ SF. Analyzed the data: ACJ BBF. Contributed reagents/materials/analysis tools: LN. Wrote the paper: ACJ. Made substantial edits to the manuscript: SF LN BBF SEL.

References


