Research Report

What goads cigarette smokers to smoke? Neural adaptation and the mirror neuron system

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ABSTRACT

One model of addiction suggests that neural circuits in the frontal cortex adapt to drug use and become sensitized leading to excessive attribution of incentive salience to drug-associated cues. The present study examined changes associated with cigarette use in the frontal mirror neuron system (MNS) of the human brain, as reflected in mu rhythm responsiveness. Mirror neurons in premotor cortex exhibit visuomotor properties that allow them to respond to self-movement as well as the observation of movement. This is a potential neural substrate for imitation learning and social cognition, factors that may be important in determining who does and does not develop addictive behaviors. EEG mu rhythm suppression is hypothesized to reflect MNS activity and thus provide a non-invasive method for studying this relationship. Our results show that while nonsmokers exhibit normal mu suppression to observed and self-generated actions, smokers exhibit normal suppression only to self-movement but not to the observation of movement, particularly actions involving addiction-related cues. Non-abstinent and abstinent smokers (those abstaining for approximately 12 h) did not differ significantly in their responses to the observation of movement, i.e., both exhibited atypical patterns of mu rhythm reactivity compared to nonsmokers. These data support the hypothesis that cigarette use produces short- and longer term adaptations in the MNS. Such adaptations may inappropriately bias attention toward motivationally salient, addiction-related cues leading to more impulsive and addiction-related behaviors.

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1. Introduction

Although the underlying neural mechanisms of addiction have yet to be fully elucidated there is substantial evidence to suggest that genetic, biological, cognitive and social factors play critical roles (Koob and LeMoal, 2001; Robinson and Berridge, 2000). Many cognitive theories of drug addiction, such as aberrant learning theories, are based on the development of conditioned associations through repeated drug exposure. These associations have been implicated in the acquisition, maintenance, and relapse of compulsive drug-taking behavior (Siegel and Ramos, 2002). Beyond pleasure and pain as mediating factors, most aberrant learning hypotheses argue that drugs produce abnormally strong or aberrant...
associations involved in reward learning, associations that are more powerful than natural reward associations. Implicit models of aberrant learning (Tiffany, 1999) explain addiction as over-learned habits that become so automatic that they essentially become compulsive (a habit-learning stimulus–response or S–R model). The formation of S–R habits, however, cannot account for the compulsive and yet flexible nature of drug-seeking behavior. It has been suggested that this requires an additional motivational explanation.

Robinson and Berridge (2000) and Robinson and Kolb (2004) have suggested that addictive drugs alter brain systems involved in motivated behavior. More specifically, drugs affect systems such as the ventral striatum, amygdala, and nucleus accumbens that are responsible for mediating the attribution of incentive salience. It is proposed that these neural circuits adapt and become hypersensitive to drugs, to their physiological effects, and to drug-associated cues. Furthermore, it is speculated that this adaptation occurs primarily through up-regulation of the mesolimbic DA system. Such 'neural sensitization' leads to excessive attribution of incentive salience to drug-related representations, inducing a psychological or compulsive wanting of the drug. Furthermore, systems mediating incentive salience can be dissociated from those that mediate the hedonic or pleasurable effects of drugs— or ‘liking’ system.

The widespread release of DA has been suggested to result in a series of adaptations in neural circuits well beyond saliency and reward and that involve motivation, drive, memory, conditioning, control and disinhibition (Robinson and Kolb, 2004; Volkow, 2004). These neural adaptations can lead to enhanced and long-lasting dysregulation of areas such as the orbitofrontal cortex (salience attribution), prefrontal cortex (judgment and inhibitory control), and cingulate cortex (inhibitory control, attention and impulsivity) among others (Volkow, 2004). It is theorized that compulsive drug taking behavior emerges from the increase in motivational drive for the drug, strengthened by conditioned responses, coupled with a decrease in judgment and inhibitory control. It is in this sense that we hypothesize that the compensatory nature of the brain’s response to drugs also leads to the neural sensitization of the frontal MNS in the human brain.

Although mirror neurons cannot be studied directly in humans, the existence of homologous cells in or near Brodmann’s area 44 has been supported by indirect population-level measures such as TMS (Fadiga et al., 1999) and fMRI (Iacoboni et al., 1999). In addition to its responsiveness to low-level, motor-related imagery, the human MNS has been implicated in higher level cognition. Rizzolatti and Craighero (2004) and Umilta et al. (2001), for example, have suggested that the capacity to associate the visual representation of an observed action with the motor representation of that action can lead to imitative learning. Oberman and colleagues recently reported evidence for a dysfunctional mirror system in high functioning individuals diagnosed with autism spectrum disorders (ASD) (Oberman et al., 2005). ASD are largely characterized by deficits in imitation, pragmatic language, theory of mind, and empathy. Other researchers have suggested that an observation/execution mechanism may underlie the hypothesized evolution of language from an earlier gestural communication system (Rizzolatti and Arbib, 1998). Still others have suggested that once another individual’s actions are represented and understood in terms of one’s own actions, it is possible to make predictions about the mental state of the observed individual, leading to “theory of mind” capabilities (Gallese, 2003). Lastly, Leslie et al. (2004) found that empathy may critically depend on one’s ability to understand the observed facial expression in terms of one’s own motor representations. In summary, all these high-level properties suggest that the MNS is part of a broader system that mediates how we relate to others in the world. Because of its critical involvement in social cognition, we suggest that a hypersensitive MNS might enhance responsiveness to immediate social cues leading to more impulsive and addiction-related behaviors.

In a review of the literature, Jentsch and Taylor (1999) argued that chronic exposure to specific drugs (including marijuana, cocaine, and amphetamine) can depress neural processing in fronto- and orbitostriatal systems involved in cognitive inhibitory control over behavior can lead to behavior unduly dominated by "pre-potent tendencies" resulting in a "condition associated with profound impulsivity that may contribute to compulsive drug-seeking and drug-taking behavior." These effects on fronto corticocortical and frontal cortico-subcortical systems are supported by clinical reports that show neuropsychological deficits in addicts are similar to those of patients suffering from prefrontal dysfunction (Bechara and Van der, 2005).

One drug that appears to produce neural adaptation is nicotine. Nicotine is a psycho stimulant that is present in tobacco and thought to be the principal agent involved in tobacco addiction. It acts as an agonist to activate and desensitize nicotinic acetylcholine receptors (nAChRs). Repeated administration of nicotine can produce behavioral and motivational sensitization (Samaha et al., 2005; Miller et al., 2001). The evidence suggests that this is due to the chronic exposure to the drug, which then leads to changes in the density of nAChRs in both humans and animals in several brain areas, including frontal cortex (Pidoplichko et al., 2004; Samaha et al., 2005). A major component of nicotine’s addictive power is its direct effects on the mesolimbic dopaminergic system. Pidoplichko et al. (2004) have identified three main actions that regulate the activity of midbrain dopamine (DA) neurons. First, nicotine activates and then desensitizes nAChRs on DA neurons. This directly excites the neurons for a short period of time before the nAChRs desensitize. Second, nicotine enhances glutamatergic excitation. Finally, nicotine decreases GABAergic inhibition. All these events increase the probability for synaptic plasticity, including long-term potentiation, with the consequence being a relatively long-lasting heightened activity of midbrain DA neurons.

\[1\] FFT (fast Fourier transform); fMRI (functional magnetic resonance imaging); MNS (mirror neuron system); nAChR (nicotinic acetylcholine receptor); S–R (stimulus–response).
The present study sought to investigate the effects of cigarette use on neural adaptation in the frontal MNS by examining individual user responsiveness to images representing motivationally, as well as socially relevant actions (i.e., those associated with the addiction) compared to visually matched neutral actions and self-movements. Because previous studies have shown that a decrease in electroencephalogram (EEG) power in the mu frequency band (8–13 Hz) recorded over motor cortex reflects MNS activity during execution and observation of motor actions, mu power activity was measured during these presentations (Pineda et al., 2000; Muthukumaraswamy et al., 2004; for a review, see Pineda, 2005). The connection between mirror neuron activity and the mu rhythm was first suggested by Altschuler et al. (1997) and thereafter by others (Oberman et al., 2005; Muthukumaraswamy et al., 2004). Mu rhythms exhibit dominant frequencies in the 8–13 Hz and 15–25 Hz bands (Salmelin and Hari, 1994). These oscillations are limited to brief periods of 0.5- to 2-s duration (Niedermeyer et al., 2004) and are recorded primarily over sensorimotor cortex in the absence of movement. At rest, sensorimotor neurons fire in synchrony leading to large amplitude EEG oscillations. When subjects perform an action, these neurons fire asynchronously, decreasing power in the mu band (Salmelin and Hari, 1994; Pfurtscheller et al., 1997). Indeed, it has been reported that mu power recorded from electrodes at scalp locations over sensorimotor cortex is reduced in normal adults by self-initiated movement, imagined movement, and observed movement (Gastaut and Bert, 1954; Cochin et al., 1998; Pineda et al., 2000).

2. Results

2.1. Behavioral performance

Counting accuracy for all subjects was 100% indicating that while the counting task was easy, no one lost their attentional focus.

2.2. Carbon monoxide (CO) readings

CO levels for abstinent smokers showed a mean of 5.8 parts per million (ppm: range=2–14, SD=3.9), with only one subject falling 2 SD above the mean and therefore potentially not abstinent. However, this subject was included in the analysis because he was the heaviest smoker (30 cigarettes/day) and his CO reading while abstinent did fall in the expected range for such heavy use. CO readings were mainly used to verify abstinence; therefore no readings were taken during non-abstinent sessions.

2.3. Comparison of baseline conditions

There were no statistically significant effects of baseline type. That is, responses to white noise and to the inanimate ball movement (ball) were similar, F(1,23)=2.0, p=0.17. Therefore, analyses of mu ratios were carried out only relative to the white noise condition.

2.4. Broad spectrum (8–13 Hz)

2.4.1. Absolute power

Only a marginally significant smoking state by electrodes by group effect was noted for absolute power in the mu band, F(5,70)=3.4, p=0.06, with nonsmokers showing greater mean power (9.2 μV) than abstinent smokers (7.5 μV) or non-abstinent smokers (6.3 μV) across electrodes.

2.4.2. Ratio relative to white noise

There was a main effect of group, F(1,14)=8.3, p<0.02, with non-abstinent smokers showing a larger ratio (1.1) compared to nonsmokers (0.87). The log transform of those ratios showed a similar main effect of group, F(1,14)=7.1, p<0.02. Compared to nonsmokers, both groups of smokers (non-abstinent and abstinent) showed a lack of mu suppression and in fact showed slight enhancements or hypersynchrony in their responses, as illustrated in Fig. 1. There was no effect of smoking state, meaning that smoking and abstaining from it did not produce statistically significant differences (p=0.37). There was a main effect of electrodes, indicating overall larger
suppression across groups over left (C3 = −0.054) compared to right hemisphere (C4 = −0.043), F(2,28) = 3.9, p < 0.05. Electrodes by group interaction, F(2,28) = 5.82, p < 0.02 indicated that the larger difference occurred over the left hemisphere. There was also a marginally significant interaction of movement type by electrodes (F(8,112) = 2.26, p = 0.08) indicating that self-movement of the right hand tended to produce larger suppression over the left hemisphere, whereas the ‘observation’ of a moving hand produced larger suppression over the right hemisphere.

2.5. Narrow spectrum (low: 8–10 Hz and high: 10–13 Hz)

2.5.1. Absolute power
A marginally significant effect of frequency band indicated somewhat higher power for high (4.6 μV²) than for low (3.5 μV²) mu bands, F(1,1) = 3.6, p = 0.08. A highly significant frequency band by movement type interaction (Fig. 2) showed that except for the self-movement condition, the high band typically exhibited more power than the low band, with slightly larger differences occurring during goal-directed action (i.e., the crayon and cigarette videos), F(5,70) = 3.89, p < 0.02. Finally, a significant frequency band by electrodes interaction, F(2,28) = 5.09, p < 0.02, indicated that mu power was consistently greater in the high band than in the low band at all the central electrode sites (C3, Cz, C4) with greater differences occurring over left (1.84 μV²) compared to right hemisphere (1.36 μV²). No effect of smoking state occurred indicating no difference between non-abstinent and abstinent smoking conditions.

2.5.2. Ratio relative to white noise
There was an overall main effect of movement type, F(4,56) = 3.80, p < 0.05. Responses to hand, self-move, and crayon, across both bands, showed significant mu suppression relative to an absolute baseline, while the cigarette video condition showed no suppression. A band frequency by movement type interaction, shown in Fig. 3, indicates that the low band shows greater suppression to the observation of movement (hand, crayon), other than in the cigarette video condition. In contrast, the high band is most responsive to self movement.

3. Discussion

Results from the present study demonstrate that smokers, both non-abstinent and abstinent, exhibit an atypical pattern of mu rhythm reactivity compared to nonsmokers. Nonsmokers show the expected pattern of mu suppression seen in healthy adults and children in response to self-generated actions as well as to the observation of movements (Oberman et al., 2005). Mu suppression in nonsmokers was also symmetrical over left and right central sites. Furthermore, consistent with previous reports, nonsmokers showed no suppression to inanimate or ball movements (Oberman et al., 2005). In contrast, both non-abstinent and abstinent smokers showed suppression or even slight enhancement or hypersynchronization in mu power during the observation of actions. These differences tended to be larger over the left compared to the right hemisphere and larger when the movement was motivational (e.g., the observation of a hand removing a cigarette from a cigarette pack), indicating a degree of specificity for addiction-related actions. If mu rhythms reflect MNS activity then these data support the hypothesis that cigarette use produces short (non-abstinent smokers)- and longer term (in the abstinent smokers) neural adaptations in the frontal mirror neuron system of the human brain. This is consistent with one of the fundamental hypotheses in addiction research—that pharmacological properties of drugs induce aberrant neuroadaptive changes that may mediate pathological behaviors such as habitual drug use and the overwhelming desire to get drugs (Vanderschuren and Kalivas, 2000). This is also consistent with recent studies showing that both current smokers and former smokers show reduced P300 amplitudes compared to nonsmokers. Furthermore, the observation is also consistent with the observation that smokers compared to nonsmokers show hypoactivation...
EEG studies have found that the mu rhythm is modulated by fMRI studies of the human MNS, more recent (Pineda et al., 2000). Second, similar to previous functional magnetic resonance imaging (fMRI) studies of the human MNS, more recent (Pineda et al., 2000) have hypothesized the existence of a selective rhythm found in the upper alpha band (10–13 Hz). In a recent review (Pineda, 2005), it is postulated that mu wave synchronization reflects gating of information at the thalamic level. If correct, the findings in the present study suggest that cigarette smoking leads to dysfunctional thalamocortical gating, perhaps making the individual user inappropriately bias attention toward motivationally salient, addiction-related cues. This finding is consistent with research that shows that acetylcholine receptors play a critical role in the behavioral and neurological hypersensitivity that occurs during addiction (Schoffelmeer et al., 2002). Furthermore, this hypersensitivity may play a key role in the neural mechanism underlying incentive salience and drug craving. More specifically, we suggest that a hypersensitive MNS in frontal cortex (characterized by lack of desynchronization or hypersynchronization of mu rhythms) reflects a disconnection of frontal executive circuits that enhances responsiveness to immediate addiction-related cues, leading to more impulsive and addiction-related behaviors.

4. Experimental procedure

4.1. Subjects

Participants in the study were given a choice of cash compensation, experimental credit hours for cognitive science or psychology courses, or a split between the two. Of the 23 subjects (13 smokers and 10 nonsmokers), nine were female. Mean age for smokers (n=13) was 23.4 years (range=18–44, SD=8.2) with 10 right handers, and for nonsmokers (n=10) it was 18.9 years (range=18–21, SD=1.0) with 9 right handers. The differences in age between the groups are due to the inclusion of two older adults (39, 44 years) in the smokers group. At prescreening, smokers reported smoking an average of 13.5 cigarettes per day (range=5–42, SD=11.3). Eight of the smokers (6 male and 2 female; 7 right handers) returned for a second visit to participate in the abstinence condition. These abstinent smokers had a mean age of 22.9 years (range=18–44, SD=8.6) and smoked an average of 12.8 cigarettes per day (range=5–30, SD=8.6). Only eight of the nonsmokers (4 male and 6 female; 9 right handers) were, therefore, included in the data analysis. Experiment was conducted with the understanding and the written consent of each participant. The Institutional Review Board at the University of California, San Diego approved the protocol for this experiment.

4.2. Stimulus materials and design

The task was a modified version of the protocol used by Oberman et al. (2005). EEG data were collected during the viewing of five videos containing various movements and one condition in which subjects mimicked a hand movement. All videos were 80 s in length and movement in both the videos and self-movement occurred at a rate of approximately 1 Hz. All conditions were presented twice in order to obtain enough clean EEG data for analyses, and the order of conditions was
counterbalanced across subjects, with the constraint that the self-movement condition always followed the observation conditions so that the subjects had a model on which to base their action.

The black and white videos were presented on a monitor 96 cm away from the subject. The hand depicted in the videos was a right hand, medium gray (8.6 cd/m²) on a black background (3.5 cd/m²), with the image subtending approximately 5° of visual angle. The five conditions, as illustrated in Fig. 4, were: (1) baseline (white noise): visual white noise representing full-screen television static (mean luminance 3.7 cd/m²); (2) Inanimate action (ball): two light gray balls (32.0 cd/m²) were observed moving together and then back apart on a black background (1.0 cd/m²). The balls moved vertically towards each other, touched in the middle of the screen, and then moved apart to their initial starting position at a rate of about 1 Hz. The ball stimulus subtended approximately 2° of visual angle when touching in the middle of the screen and about 5° at its maximal point of separation; (3) Non-goal directed mimicking movement (hand): a hand mimicking the hand actions depicted in #4 and #5 below but without the target objects; (4) Neutral goal-directed hand movement (crayon): a hand removing a crayon from a box; (5) Motivationally salient goal directed hand movement (cigarette): a hand removing a cigarette from a cigarette pack; and (6) Self-movement: subjects performed a similar hand movement with their right hand as observed in #3 above (non-goal directed mimicking movement).

To ensure that subjects maintained attention on the video stimuli throughout the observation task, they were asked to engage in a continuous performance task. Between four and six times during the 80-s video, the stimuli stopped moving for approximately one cycle (a period of 1 s). Subjects were asked to count the number times stimuli stopped moving and to report their count upon completion of the trial block.

Each subject was scheduled as early as 9:00 AM or as late as 2:30 PM, depending on the individual’s availability. Instructions for subjects during the non-abstinence sessions were to avoid any disruption of their smoking routine prior to their laboratory visit, but that no smoking would occur during the experiment itself. Eight of the smokers returned on a separate day for the abstinence condition; hence abstinence always followed non-abstinence sessions. Subjects abstained from smoking for 12 h before arriving at the laboratory. This deprivation period is consistent with many other abstinence studies. EEG preparation took approximately 30 min, so that by the time subjects began the task, they had been smoking abstinent for about 12.5 h. Subjects were informed that upon arrival at the laboratory for each session they would be asked to report on their recent smoking behavior, and that they would need to provide an expired breath sample using a carbon monoxide (CO) monitor to verify smoking abstinence. On arrival, subjects gave informed consent to participate and took the CO test.

4.3. Data acquisition and analysis

Subjects were fitted with electrodes and shown their free-running EEG on the acquisition computer to facilitate compliance with instructions to fixate vision and restrict movement. Neuroscan SCAN 4.2 software and SynAmps amplifiers were used to record continuous EEG from 13 channels (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, T5, T6, O1, and O2), arranged according to the International 10–20 system. Ag/AgCl skin surface electrodes placed approximately 2 cm above and below the left eye recorded the vertical electrooculogram (vEOG). Electrodes placed behind each ear (mastoid bones) were electronically linked and served as the reference electrode. Electrical impedance was held to less than 5 kΩ for all EEG scalp sites and below 10 kΩ for vEOG. Once the electrodes were in place, subjects were seated inside an electrically and acoustically shielded testing chamber.

Fig. 4 – Five observation conditions consisting of: (1) static white noise as the baseline condition (White Noise); (2) Inanimate action consisting of two gray balls moving together and apart (Ball); (3) non-goal directed mimicking movement of a hand opening and closing (Hand); (4) neutral hand movement of a hand removing a crayon from a box (Crayon); and (5) a motivationally salient movement of a hand removing a cigarette from a cigarette pack (Cigarette).
Both EEG and vEOG were amplified with a bandpass filter of 0.05 to 30 Hz, and sampled at 500 Hz. Ocular artifacts in the continuous EEG for each subject were removed off-line through the automatic application of a voltage threshold procedure provided in SCAN 4.2 software. EEG was then epoched, and baseline-adjusted. Because EEG oscillations in the 8–13 Hz frequency range are influenced by states of expectancy and awareness, and since the mu frequency band overlaps with the posterior alpha band, it is possible that recordings from C3, Cz, and C4 might be affected by this posterior activity, which is more related to visual processing. Therefore, the first and last 10 s of each block of data were removed from all subjects to eliminate the possibility of attentional transients due to the initiation and termination of the stimulus. A 1-min segment of data following the initial 10 s was obtained and combined with the other trial of the same condition, resulting in one 2-min segment of data per condition.

Data were analyzed only if there were sufficient “clean” data with no movement or eye blink artifacts. For each cleaned segment, the integrated power in the 8–13 Hz range was computed using a Fast Fourier Transform (FFT). Data were segmented into epochs of 2 s beginning at the start of the segment. FFTs were performed at 0.5 Hz intervals on the epoched data (1024 points). A cosine window was used to control for artifacts resulting from data splicing. The broad spectrum analysis was complemented with ones in which frequencies were divided into low (8–10 Hz) and high (10–13 Hz) mu bands since previous studies have indicated the existence of at least two types of mu rhythms.

Several measures of mu suppression were calculated. First, mu rhythm activity was quantified by determining overall power in the raw EEG for either the broad spectrum (8–13 Hz) or for the 8–10 Hz (low) or 10–13 Hz (high) bands. Second, the ratio of the power during the observed and self-movement conditions relative to the power during the baseline white noise condition was computed. A ratio was used to control for variability in absolute mu power as a result of individual differences such as scalp thickness and electrode impedance, as opposed to strictly mirror neuron activity. A ratio of less than one indicates suppression whereas a value of one indicates no suppression and values greater than one indicate enhancement. Since ratio data are inherently non-normal as a result of lower bounding, a log transform was also used for analysis. A log ratio of less than zero indicates suppression whereas a value of zero indicates no suppression and values greater than zero indicate enhancement. Third, the ratio of the power during the observed and self-movement conditions relative to the power in the ball condition was computed. Responses to both baseline conditions (the white noise and the ball movement) were compared to determine whether control for attention to counting or any effects due to stimulus stopping during the continuous performance task affected the data.

Analyses of absolute power in the full spectrum frequency band used a repeated measures analysis of variance (ANOVA) with smoking status (non-abstinence, abstinence), movement type (baseline, ball, hand, self-movement, crayon, cigarette) and electrodes (C3, Cz, C4) as within-subjects factors and group (smokers, non-smokers) as a between-subjects factor. Analyses of ratio and log-transformed ratio data used a similar repeated measures ANOVA but with only five movement types. Finally, analyses of the narrow mu bands included a band frequency factor (low, high). Geisser–Greenhouse corrections were applied to the degrees of freedom with only the corrected probability values reported. When significant differences were found, the Tukey–Kramer Honestly Significant Difference test was used for pairwise comparisons.

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