Dorsolateral prefrontal and orbitofrontal cortex interactions during self-control of cigarette craving

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Drug-related cues induce craving, which may perpetuate drug use or trigger relapse in addicted individuals. Craving is also under the influence of other factors in daily life, such as drug availability and self-control. Neuroimaging studies using drug cue paradigms have shown frontal lobe involvement in this contextual influence on cue reactivity, but have not clarified how and which frontal area accounts for this phenomenon. We explored frontal lobe contributions to cue-induced drug craving under different intertemporal drug availability conditions by combining transcranial magnetic stimulation and functional magnetic resonance imaging in smokers. We hypothesized that the dorsolateral prefrontal cortex (DLPFC) regulates craving during changes in intertemporal availability. Subjective craving was greater when cigarettes were immediately available, and this effect was eliminated by transiently inactivating the DLPFC with transcranial magnetic stimulation. Functional magnetic resonance imaging demonstrated that the signal most proportional to subjective craving was located in the medial orbitofrontal cortex across all contexts, whereas the DLPFC most strongly encoded intertemporal availability information. The craving-related signal in the medial orbitofrontal cortex was attenuated by inactivation of the DLPFC, particularly when cigarettes were immediately available. Inactivation of the DLPFC also reduced craving-related signals in the anterior cingulate and ventral striatum, areas implicated in transforming value signals into action. These findings indicate that DLPFC builds up value signals based on knowledge of drug availability, and support a model wherein aberrant circuitry linking dorsolateral prefrontal and orbitofrontal cortices may underlie addiction.

decision making | smoking | nicotine | expectancy | temporal discounting

Addiction can be placed within the framework of decision making (1, 2). Drug cues such as the sight or smell of cigarettes can trigger craving and drug seeking (3, 4). Behavioral economists propose that drug cues increase the marginal utility of the drug, favoring the decision to consume (3, 5, 6). Indeed, cue-induced craving reflects the subjective value of drug use (7) and predicts drug-seeking behaviors (8, 9), but is also amenable to self-control (6, 10). Cue-induced craving is affected by a variety of contexts and events that impact self-control, such as perceived drug availability (11–14), expectancy (15), stress (16), or intention to seek treatment (17). However, the mechanism by which craving is under the regulation of self-control is poorly understood both at behavioral (17) and neural levels (1, 18).

The perceived opportunity to use a drug increases the craving response to drug cues and may itself be viewed as a conditioned cue (17). Recent studies indicate that cigarette craving is influenced to a greater degree by cognitive expectancy to smoke than by nicotine withdrawal (11–13). For example, flight attendants on nonsmoking flights reported higher craving urges immediately before landing, when smoking was about to be permitted, independently of the duration of abstinence (11). The evidence, however, is that expectancy only invokes craving in the presence of a conditioned smoking cue (12, 15).

Neuroimaging studies in addiction have revealed cue-related responses in numerous brain areas, including frontal, visual, and parietal cortices and subcortical areas (18, 19), but none has investigated the neural substrates of the incorporation of contextual information into craving. A metaanalysis of the cue reactivity neuroimaging literature suggested that prefrontal cortical areas are only activated when drug use is available soon after the scanning procedure (18), but did not specify how context is processed within prefrontal circuitry. Recent studies suggest involvement of dorsal or medial prefrontal cortex in cognitive control of craving (20, 21), although causal roles of these areas has not been demonstrated.

We hypothesize that cue-induced craving is a reflection of the current net value of the drug for the addicted individual, as a function of drug cues and drug-related context, and may be encoded in the medial orbitofrontal cortex (mOFC). This is based on recent findings that the mOFC encodes subjective value for available goods after accounting for variables such as temporal delay, risk, and cost (22–25). We also hypothesized that information regarding the immediacy of drug availability may be processed in circuitry including the dorsolateral prefrontal cortex (DLPFC). This hypothesis derives from recent literature on the critical role of the DLPFC in intertemporal choice (26, 27) and self-control (28, 29). Specifically, our hypothesis arises from our previous work in smokers performing a cigarette cue task, in which craving-related signals were greater in an area of left DLPFC when cigarettes were available immediately compared with when they were available later (30). In the current study, we tested this hypothesis using a within-subject design of behavior and functional magnetic resonance imaging (fMRI) with or without transient focal inactivation of the left DLPFC. Cortical inactivation was achieved using 1-Hz transcranial magnetic stimulation (TMS), which is known to transiently inhibit the targeted cortex (31). The results of behavioral and neuroimaging data, combined with inactivation of the DLPFC, shed light on the ways in which cues and context are combined to drive smoking behavior.

Results

The fMRI study comprised a within-subject 2 × 2 factorial design with factors of "cigarette availability" and "TMS," as illustrated in Fig. 1*A* (detailed in *Materials and Methods* and *SI Text S1*). Each subject underwent four sessions of the fMRI smoking cue reactivity task on different days, with the order of sessions randomized and counterbalanced across subjects. The cue reactivity task comprised a block design that included two types of videos, one of individuals engaged in cigarette smoking, and a control video of persons engaged in nonsmoking behavior (30). The two

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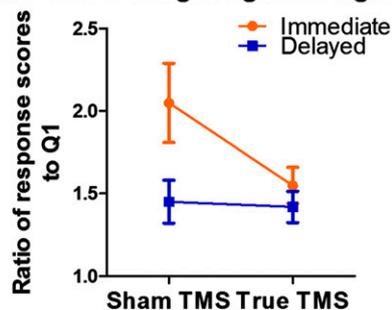**Fig. 1.** Study design and behavioral response to cues. (*A*) Each subject underwent four sessions of the cue reactivity task during functional magnetic resonance imaging (fMRI) with transcranial magnetic stimulation (TMS) on different days. Sessions differed in terms of drug availability (delayed by 4 h; immediate) and TMS (sham TMS; true TMS), constituting a 2 × 2 factorial design. After being informed about cigarette availability, subjects received true or sham TMS of left dorsolateral prefrontal cortex (DLPFC) in a single-blinded manner, followed by fMRI scanning during the cue reactivity task that includes exposure to neutral and smoking videos, and a four-item questionnaire after each video. (*B*) Behavioral response to cues (craving). Plot of mean ratios of scores for craving between smoking and neutral videos. Error bar indicates SEM. See also *SI Text S2* for details.

cigarette availability conditions differed as follows: (*i*) subjects were told before scanning that they should not smoke for 4 h after the fMRI scan and that this would be verified by carbon monoxide (CO) breath test (delayed availability condition); and (*ii*) subjects were told they could smoke immediately after the fMRI scan (immediate availability condition). In a previous fMRI study, we had found that the craving-related signal in the left DLPFC was significantly greater in the immediate compared with the delayed condition (30). The two TMS conditions consisted of sham TMS and true TMS targeted at the left DLPFC site identified in our previous study, administered in a single-blind manner immediately before fMRI acquisition. The extent of the physiological effect of TMS as used here is thought to be ~1 cm, based on positron emission tomography (32) and electrophysiological (33) studies. We confirmed that the actual targeted area for each subject was within 1 cm of the intended target. TMS was administered in a room adjacent to the MRI suite for a total duration of ~35 min. After TMS, subjects were asked to immediately move to the MRI suite to undergo an fMRI scan for a period of 15.5 min. The time interval from the end of TMS stimulation to the end of fMRI acquisition was 21.4 ± 1.3 min varying from 19.5 to 25.5 min, which was less than the expected duration of inhibitory effects

from our TMS paradigm (at least 30–60 min) (31, 34). Exhaled CO monitoring 4 h later confirmed that participants complied with the instructions of cigarette availability.

Behavioral Data. Subjects indicated their current level of craving (Q1, "I'm craving a cigarette right now") after each video using a visual analog scale. Relative craving was significantly affected by the interaction of availability and TMS [$F_{(1,9)} = 6.3$, $P < 0.05$] (Fig. 1*B*), but there was no significant effect of availability or TMS. Relative craving differed between the two availability levels in sham TMS [$T_{(9)} = 2.8$, $P < 0.05$] but not in true TMS [$T_{(9)} = 1.4$, $P = 0.2$]. These findings indicate that craving is amenable to modulation by cues and contextual information (intertemporal cigarette availability), and that inactivation of the DLPFC with TMS eliminated the effect of cigarette availability on craving. Detailed behavioral data are provided in *SI Text S2*.

Neural Activity Associated with Cue-Induced Craving. There was significantly greater blood oxygen level-dependent (BOLD) activity during the smoking compared with the control video in several brain areas including the bilateral DLPFC, medial prefrontal cortex, frontal pole, ventral striatum, and temporal, parietal, and visual cortices (Fig. S1*A* and Table S1), in keeping with our previous study (30). We then looked for brain areas where activity correlated with subjective cigarette craving. We identified relatively localized areas of the prefronto-striatal circuitry, with the greatest effect size located in the mOFC, followed by the left DLPFC and ventral striatum (cluster-corrected $P < 0.05$; Fig. 2*A* and Table S2). The mOFC BOLD signal correlated only with craving and was not influenced by any of intention to smoke, irritability, boredom, or by cue alone (Table S2). Intention to smoke correlated with BOLD signal in the dorsolateral and dorsomedial cortices, inferior parietal lobule, and putamen (Fig. S1*B* and Table S2), whereas subjective irritability and boredom were not correlated with brain activity (Table S2).

These behavioral and neural findings support our first prediction that the subjective value of cigarette smoking is a function of availability and cues, and that it is encoded in the mOFC. Because cue-induced craving is known to be variable across individuals in terms of both ease of elicitation and magnitude (35), we further explored whether the intersubject variance in craving was reflected in intersubject variation in the BOLD signals in the mOFC. Craving-related BOLD signals were obtained from the sham TMS sessions and regressed against the relative subjective craving level. The individual variation in the mOFC signal was significantly explained by the subjective variance in craving in both the immediate [$F_{(1,8)} = 13.4$, $P < 0.01$] and delayed condition [$F_{(1,8)} = 7.2$, $P < 0.05$] as shown in Fig. 2*C*, indicating that mOFC activity reflected the subjective valuation of drug-related stimuli.

Neural Activity Associated with Intertemporal Cigarette Availability. We found significantly increased craving-associated BOLD signal in the immediate relative to the delayed condition in dorsal prefrontal areas, with the highest effect located in the left DLPFC (Fig. 2*D* and Table S3) at *x, y, z* = –38, 32, 40 (*Z* = 4.66). The location was within 10 mm of our intended TMS target (Fig. 2*D*, S2*A* and *B*), within the expected spatial extent of the physiological effect of TMS (~1 cm) (32, 33). A significant, but smaller, effect of availability was also found in the medial and central orbitofrontal cortex, ventral striatum, and inferior temporal gyrus (Table S3). There was no effect of availability on the left DLPFC signals related to intention, boredom, irritability or cues alone (Table S3). These results replicate our previous study (30), but more specifically correlate craving-related brain activity in DLPFC with intertemporal availability.

Effect of TMS on Cue-Induced Neural Activity. We also found a significant TMS by availability interaction effect on craving-
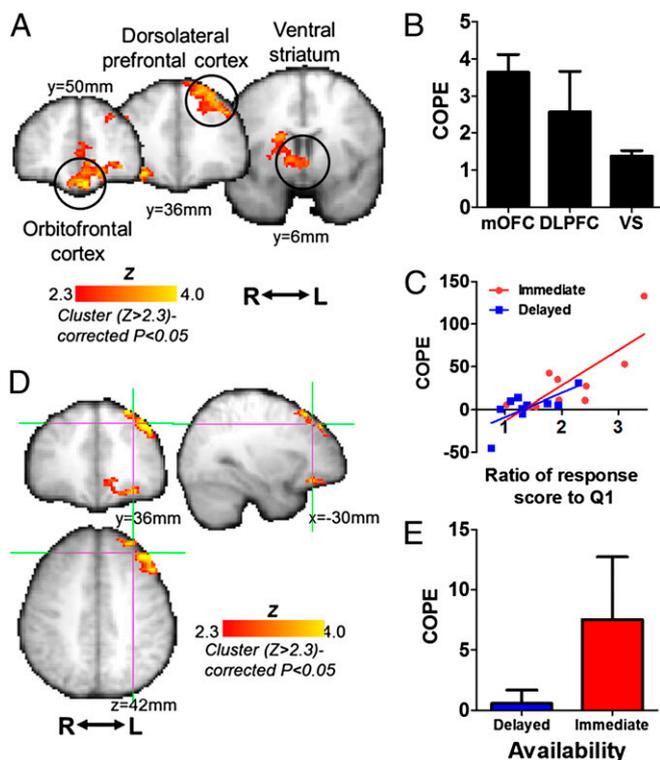
Fig. 2. Neural activity related to craving and intertemporal cigarette availability. (*A*) Areas of significant correlation of blood oxygen level-dependent (BOLD) signals with craving ratings (Q1 "I'm craving a cigarette right now") in the first level multiregression analysis of the fMRI data for all four conditions combined. The highest correlation was found in the medial orbitofrontal cortex (as shown in the slice at *y* = 50 mm). (*B*) Effect size [contrast of parameter estimates (COPE)] at the peak of the medial orbitofrontal cortex (mOFC) (centered at *x, y, z* = −4, 46, −22 mm), dorsolateral prefrontal cortex (DLPFC) (*x, y, z* = −30, 36, −40 mm), and ventral striatum (VS) (*x, y, z* = 12, 4, 0 mm). All peaks are listed in Table S2. See also Fig. S1*A* and Table S1 for the cue-induced BOLD signal increase and Fig. S1*B* for the correlation with intention to smoke (Q3). (*C*) Effect size [contrast of parameter estimates (COPE)] of the craving-associated contrast at mOFC (*x, y, z* = −4, 46, −22 mm) correlated with the subjective craving ratio (smoking minus neutral, averaged within each session) in the sham TMS conditions. (*D*) Areas of significant effect of drug availability (immediate > delayed) on craving-associated brain activation. The largest effect was found in the left DLPFC, which was close to the target of TMS (indicated by a crosshair). (*E*) Average contrast of craving-correlated BOLD parameter estimates from the general linear model, obtained at the left DLPFC (centered at *x, y, z* = −38, 32, 40 mm), plotted against drug availability. Error bars indicate SEM. In both *A* and *B*, statistical results are shown at a threshold of cluster (*Z* > 2.3)-corrected *P* < 0.05. The maximum statistical values within 10-mm-thick volumes were axially projected onto the center slice for visualization. All peaks are listed in Table S3. See also Fig. S2*A* for the subject-by-subject location of TMS target, Fig. S2*B* for the subject-by-subject effect of availability, and Fig. S2*C* for the cue-induced BOLD signals in the target area.

associated BOLD signal in the mOFC (cluster-corrected *P* < 0.05; Fig. 3*A* and Table S5). In this area, the BOLD signal displayed a higher correlation with craving in the immediate availability condition than the delayed condition during sham TMS sessions, but this difference was reduced by true TMS (Fig. 3*A*, bar graph). Thus, the neural effect of TMS paralleled its psychometric effect (Fig. 1*B*). These data suggest that craving-correlated signals normally processed by the mOFC are amenable to modulation by inputs from the DLPFC that carry information on cigarette availability.

In addition, we analyzed the effect of TMS alone on the craving-associated BOLD signal. TMS decreased craving-associated

signals in the dorsal anterior cingulate cortex (cluster-corrected *P* < 0.05; Fig. S1*C*), indicating that activity in this area may depend on both craving and input from the DLPFC. We also tested the effect of TMS at the TMS target itself in detail. Consistent with previous literature (36), neither a whole-brain search, nor a restricted volume-of-interest analysis showed evidence of a TMS effect on craving-associated activity in the left DLPFC (Fig. S2*C*). This negative finding is addressed in *SI Text S3*.

Psychophysiological Interaction. Finally, we performed a psychophysiological interaction analysis to measure DLPFC functional connectivity while participants watched the smoking video. TMS and availability interactively altered functional connectivity of the DLPFC with the mOFC (Fig. 3*B*) and the dorsal anterior cingulate cortex (Fig. S1*D*, thresholded by a cluster of > 30 voxels, uncorrected *P* < 0.05; Table S6). In these two areas, functional connectivity with the left DLPFC was greater during the immediate compared with the delayed availability condition, and this effect was reduced by TMS (Fig. 3*B*, left bar graph). In the inverse contrast, we found altered functional connectivity in the ventral striatum (Fig. 3*B* and Table S6), such that functional connectivity of the DLPFC was reduced during immediate compared with delayed availability during sham TMS, with the effect again reduced by TMS (Fig. 3*B*, right bar graph).

Discussion

Recent work influenced by behavioral economics has shown that cue-induced drug craving is a predictor of subjective value of drug (7) and drug-seeking behaviors (8, 9), but is also amenable to contexts that engage self-control, such as drug availability (11–13), religious norms (14), expectancy (15), stress (16), and treatment seeking (17). Moreover, craving, like the economic value of goods, is amenable to delayed discounting, as shown here and elsewhere (11). Thus, craving may be in effect a reflection of the net subjective value of the drug. The current study borrows from recent models of decision making (37, 38) to map the neural representation of cue-induced craving and the role of prefrontal areas in cue reactivity and self-control, with a particular focus on the DLPFC (30). The results can be summarized in five points: (*i*) cigarette cues cause cigarette craving, with the effect potentiated by knowledge of immediate availability; (*ii*) cues activated distributed frontal areas, in which the signal in mOFC had the highest correlation with craving across contexts and subjects (Fig. 2*A*), whereas the signal in DLPFC was the most associated with intertemporal availability (Fig. 2*D*); (*iii*) inactivation of left DLPFC eliminated the potentiating effect of immediate availability on craving (Fig. 1*B*) and on the craving-related signal in the mOFC (Fig. 3*A*); (*iv*) inactivation of DLPFC also affected craving-related signals in the dorsal anterior cingulate cortex (Fig. S1*C*); and (*v*) inactivation of DLPFC and availability interactively affected the functional connectivity of the DLPFC with several craving-associated regions, namely the mOFC, ventral striatum, and anterior cingulate (Fig. 3*B* and Fig. S1*D*).

The behavioral results indicate that the perception of immediate drug availability enhances cue-induced craving, which in turn may be interpreted as temporal discounting of drug use value during delayed availability. In our within-subjects study, intertemporal availability was not a direct effector of craving, but acted to modulate reactivity to drug cues (Fig. 1*B*). This is consistent with a model (Fig. 3*C*) according to which perceived drug use opportunity acts as a conditioned stimulus that sets the occasion for drug use, but only reveals itself via an influence on cue-induced reactivity, and not on craving itself (12, 15). Our results further suggest that this modulatory effect appears to be exerted via the left DLPFC. This is consistent with a recent behavioral study in which intertemporal choice was modulated by low-frequency repetitive TMS over the left DLPFC (29). TMS did not affect
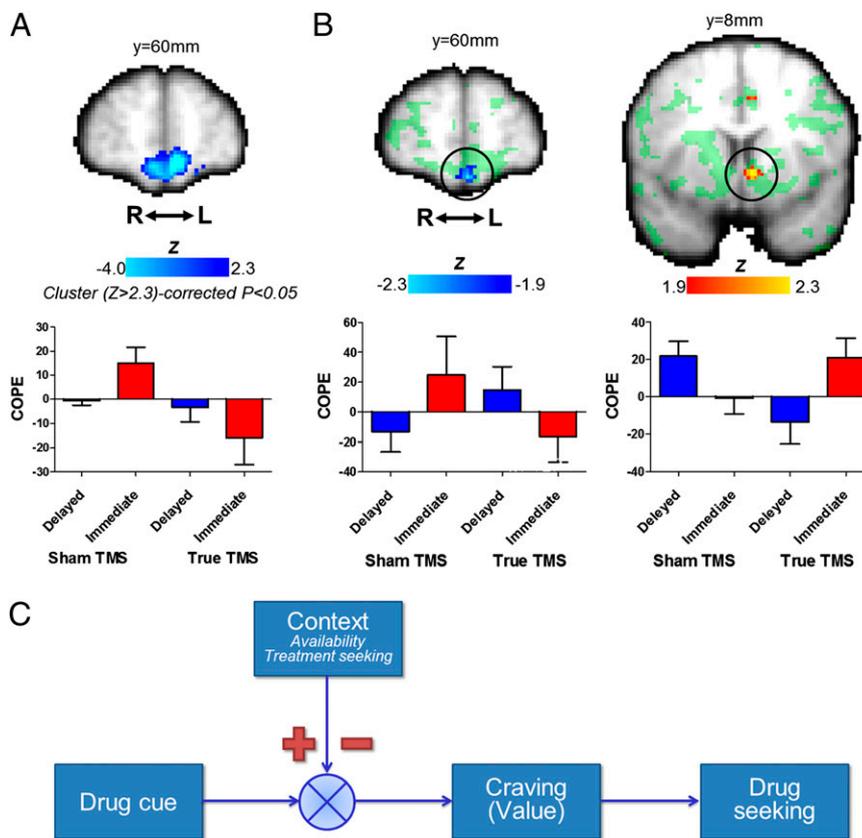
Fig. 3. Effect of transcranial magnetic stimulation (TMS) on availability and craving-associated activity, and on availability and cue-associated functional connectivity. (*A*) Effect of interaction between TMS and drug availability in the higher level analysis of craving-associated contrasts. In the medial orbitofrontal cortex, BOLD signals were affected by craving, drug availability, and TMS (light blue–blue area, cluster-corrected $P < 0.05$). The bar graph shows the mean parameter estimates from the second-level general linear model in the medial orbitofrontal cortex (centered at x, y, $z = -4$, 64, -14 mm), plotted against drug availability and TMS conditions. COPE, contrast of parameter estimates. All peaks are listed in Table S5. See also Fig. S1C and Table S4 for the main effect of TMS on craving-associated contrasts. (*B*) Areas where functional connectivity with dorsolateral prefrontal cortex (DLPFC) was significantly affected by TMS and drug availability during viewing of smoking cues. The peaks of negative contrast (light blue–blue, cluster size > 30 voxels, $Z < -1.96$) are located in the medial orbitofrontal cortex (mOFC) (*Left*), and those of the positive peak (yellow–red, cluster size > 30 voxels, $Z > 1.96$) in the ventral striatum (*Right*). The areas of altered functional connectivity are superimposed on the mask extracted from craving-associated whole-brain analysis (transparent green, $Z > 1.6$). The bar graphs below show mean parameter estimates of correlated BOLD signals with L-DLPFC target obtained from mOFC (centered at x, y, $z = -10$, 62, -18 mm), and ventral striatum (-6, 8, -4), plotted against two factors (TMS and drug availability). Error bars indicate SEM. All peaks of functional connectivity analysis are listed in Table S6. See also Fig. S1D for the result of functional connectivity found in the anterior cingulate cortex. COPE, contrast of parameter estimates. (*C*) Proposed neuropsychological model of drug cue-induced craving. Drug cues induce craving, thought here to be a value signal processed in the mOFC. This value signal is amenable to modulation based on context, a process likely enacted by the DLPFC.

valuation itself in their choice task (29), consistent with our findings that TMS had no direct influence on craving per se.

The neuroimaging findings provide two insights into how the DLPFC and mOFC interact during drug craving and intertemporal availability (Fig. 3C). First, the mOFC tracked the subjective value of the drug, as indexed by craving self-reports, whereas the DLPFC appeared to incorporate intertemporal availability and cue information to modulate the presumed mOFC value signal. Such a two-stage process of cue reactivity is consistent with recent models of frontal decision-making circuitry (26, 37), in which ventral prefrontal cortex encodes subjective value that drives decisions, whereas the dorsal prefrontal cortex tracks the state of the environment, including rules and contexts, to guide decisions. Although our findings of craving-related signals in the mOFC parallel the addiction literature (30, 39–43), a notable finding is the consistent correlation with craving under different contexts. The neural signal in the mOFC encoded this net value of drug at any given moment, as it does valuation of monetary rewards (22, 23), preferred goods (24), or charitable decisions (25). In contrast, the DLPFC signal appears to be sensitive to the context of drug use as inactivation of the DLPFC eliminated the ability of contextual

information to affect both craving and its related signal in the mOFC. The results provide evidence that the DLPFC region processes intertemporal availability to influence valuation of drug, consistent with reports of sensitivity of the DLPFC to intertemporal choice information (26, 27, 29). Second, our results demonstrate that the DLPFC can have a potentiating effect on craving and related signals in addition to the previously suggested role of DLPFC top–down signals in down-regulating brain areas that encode reward value with respect to drug use (44). Our results may support addiction studies showing cue-related activity in dorsolateral prefrontal areas only in individuals not seeking to quit drug use (18). This prefrontal potentiation of craving appears to be exerted via modulation of craving-related signals in the OFC, as the functional connectivity between the DLPFC and mOFC was dependent both on the drug cue and availability. This functional connectivity is consistent with the known existence of anatomical connections between DLPFC and mOFC based on work in primates (45, 46). It is also in line with a previous study in which self-control related to healthy food choices was associated with functional connectivity between the DLPFC and mOFC (28).

Cue-induced craving may also depend on activity in brain areas involved in computing multiplexed decision variables, including action costs and stimulus values, namely the anterior cingulate cortex and ventral striatum. Here, inactivation of the DLPFC by TMS attenuated craving-associated activity in the anterior cingulate cortex (Fig. S1C). Accumulating evidence suggests that the dorsal anterior cingulate cortex not only generates signals of stimulus value, much like the mOFC, but also signals of rewarding actions and action costs (47, 48). Moreover, a recent study showed that higher cue reactivity in the anterior cingulate cortex predicted subjects' subsequent failure to quit smoking (20). The functional connectivity between the DLPFC and anterior cingulate cortex found here (Fig. S1D) is consistent with previous observations in patients with lateral prefrontal lesions (49), a metaanalysis of functional connectivity (50), the effect of DLPFC TMS on anterior cingulate blood flow (51), and with the description of anatomical connections in primates (46, 52). The ventral striatum is another key structure in addiction (53) and is a key node in converting incentive signals into action (54) and in processing reward value (22). Primate studies have also demonstrated action value signals in the striatum (55). Our results indicate that activity in this area is consistently correlated with craving (Fig. 2A), but again under the influence of the DLPFC (Fig. 3B). Indeed, a recent fMRI study showed that, when smokers suppressed their urge to smoke, modulation of cue-induced signals in the ventral striatum was mediated by the DLPFC (21).

Our findings have implications for current debates on psychopathological models of addiction. Some [e.g., Robinson and Berridge (56)] have proposed that drug cues acquire incentive salience, or increased value, via activation of midbrain dopaminergic projections such as the medial OFC and ventral striatum. Others [e.g., Jentsch and Taylor (44)] have proposed that a dysfunctional lateral prefrontal cortex allows disinhibition of motivated drug-seeking behaviors. Our results support both models in that craving level was associated with activity in valuation/motivation circuitry, notably the OFC and ventral striatum, and activity of this circuitry was subject to higher-level input from the DLPFC. However, our study provides a distinct view in that the afferents from DLPFC do not only support self-control and inhibition, but more generally modulate mesolimbic value signals up or down based on goals and context. Additionally, a major contributor to relapse in addiction is stress (16), which is also known to cause acute and chronic impairments in prefrontal cortex function (57). Indeed, in a previous study using the same cue reactivity paradigm, we demonstrated that acute psychosocial stress increased mesolimbic responses to drug cues (58). We propose that aberrant interactions between frontal executive and valuation systems may underlie the response to drug cues in a variety of situations.

Here, we assume that our instructions to the subjects regarding availability affected subjects' expectancy to smoke cigarettes. However, no explicit measures of expectancy were obtained during cue exposure. This subjective state is difficult to measure with accuracy. Thus, it was important to ensure that the manipulation of expectancy was credible to the participants (59). Therefore, we repeatedly emphasized cigarette availability to subjects before TMS and before fMRI at every session. We did not measure the actual amount of cigarette use following each session, beyond confirming the 4-h abstinence with CO monitoring, because the current TMS settings do not, presumably, have such a lasting effect. Postscan cigarette consumption could be tested in the future with more powerful inhibitory paradigms, e.g., theta burst stimulation, which appears to have effects lasting several hours (31).

In conclusion, the within-subject, hypothesis-driven experiment presented here establishes the role of the DLPFC in integrating higher-level contextual factors with subjective craving processed in the mOFC. The findings shed light on the role of dorsolateral and ventral prefrontal areas in addiction and provide a bridge between neural models of drug addiction and decision making. In particular, the current findings dovetail with a view of addiction as a manifestation of steep temporal discounting, in which addicted individuals consistently place greater value on immediate over delayed rewards (60). The model also provides a rational basis for therapeutic mechanisms, such as cognitive behavioral therapy (53) or transcranial stimulation of the DLPFC (61, 62).

Materials and Methods

Ten otherwise-healthy moderate-to-heavy smokers aged 23 ± 3 y underwent an fMRI cue reactivity task (30) on four occasions. Subjects smoked one cigarette 30 min prior to the TMS session. They viewed 2-min video clips of smokers (smoking video) alternating with matched video clips that contained no smoking content (neutral video), and rated their subjective craving level immediately after each video clip by a visual analog scale. Compliance with an abstinent state after the two delayed availability fMRI sessions was verified 4 h postscan using a CO monitor (Vitalograph). fMRI data were hierarchically analyzed based on a mixed-effects general linear model using FSL 4.1 (www.fmrib.ox.ac.uk/fsl). The coordinates of the TMS target in the left DLPFC were defined in Montreal Neurological Institute (MNI) space based on our previous study (MNI coordinates, x, y, $z = -30$, 36, 42 mm) (30), where a significant interaction had been found between craving and availability, an effect that was replicated in the current participants (Fig. 2D and Fig. S2B). The TMS target was located in native space by using a noninvasive frameless stereotaxic apparatus (BrainSight; Rogue Research) (63). Repetitive stimulation (1,800 pulses) was delivered at low frequency (1 Hz) using a MagStim stimulator (MagStim). Low-frequency repetitive TMS is known to disrupt the target cortex for at least 30 min (34, 36). Details of subjects, TMS, fMRI, and data analysis are described in SI Text S1.

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