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Neuroimaging craving: urge intensity matters

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ABSTRACT

Functional neuroimaging has become an increasingly common tool for studying drug craving. Furthermore, functional neuroimaging studies, which have addressed an incredibly diverse array of questions regarding the nature and treatment of craving, have had a substantial impact on theoretical models of addiction. Here, we offer three points related to this sizeable and influential body of research. First, we assert that the craving most investigators seek to study represents not just a desire but a *strong* desire to use drugs, consistent with prominent theoretical and clinical descriptions of craving. Secondly, we highlight that, despite the clear conceptual and clinical emphasis on craving as an intense desire, brain imaging studies often have been designed explicitly in a way that reduces the ability to generate powerful cravings. We illustrate this point by reviewing the peak urge levels endorsed by participants in functional magnetic resonance imaging (fMRI) studies of cigarette craving in nicotine-deprived versus non-deprived smokers. Thirdly, we suggest that brain responses measured during mild states of desire (such as following satiety) differ in fundamental ways from those measured during states of overpowering desire (i.e. craving) to use drugs. We support this position by way of a meta-analysis revealing that fMRI cue exposure studies using nicotine-deprived smokers have produced different patterns of brain activation to those using non-deprived smokers. Regarding brain imaging studies of craving, intensity of the urges matter, and more explicit attention to urge intensity in future work has the potential to yield valuable information about the nature of craving.

Keywords Cigarette, craving, cue-exposure, cue-reactivity, fMRI, neuroscience, smoking.

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INTRODUCTION

Functional neuroimaging has become one of the most widely used tools for studying drug addiction [1]. In particular, an enormous amount of functional neuroimaging research has focused on drug craving, a construct that has been central to the study of addiction for more than half a century [2]. Huge sums of money are spent each year on functional neuroimaging experiments that relate to craving, as evidenced by the proliferation of such studies since our review of the literature a decade ago [3]. This now sizeable (and still rapidly growing) literature includes basic investigations designed to understand the neural architecture of craving [4], translational studies testing a range of pharmacological and psychological treatments designed to curb cravings [5] and expensive protocols aimed at evaluating genetic moderators of craving [6]. These examples, which provide only a narrow sampling of this work, reveal both the clinical and theoretical importance of functional neuroimaging research on craving [1,2].

Here, we offer three points related to this expansive and influential body of research. First, we suggest that these studies as a whole have been aimed at shedding light on craving that is best conceptualized as an intense and overwhelming desire—and not simply any desire—to use drugs [2,7,8]. Secondly, we point out that, despite the clear focus on craving as a particularly strong desire from both scientific and clinical perspectives, many studies have been designed in such a way that precludes the ability to provoke strong desires. Specifically, using functional magnetic resonance imaging (fMRI) research examining cue-elicited desire to smoke as a prevalent and representative subset of the literature, we find that studies have often produced a relatively modest desire state because they create satiety by requiring participants

to smoke a cigarette just prior to conducting their tests. Thirdly, we contend that mild desire differs in fundamental ways from the strong desire state that characterizes conceptually and clinically meaningful craving [2], much as a mild fear is distinct from a full-blown panic attack. In support of this view, we conduct a quantitative meta-analysis of fMRI smoking cue exposure studies to reveal that they have produced different results according to the degree of deprivation required of participants at the outset. Stated differently, urge intensity matters. We propose that a greater focus on urge intensity has the potential to provide insight into some of the most significant questions currently being debated in the experimental drug craving field. Our overarching goal is to stimulate discussion regarding the need to be more mindful of how craving is manipulated and measured in functional brain imaging research.

CRAVING IS WIDELY VIEWED AS AN OVERPOWERING STATE OF DESIRE

A review of the language used in functional neuroimaging studies incorporating cue–reactivity methods (i.e. exposing addicted individuals to drug-related stimuli) makes clear that investigating the nature of a subjective craving experience has been an important—and often primary—goal of this research. For example, with few exceptions, studies have highlighted the clinical significance of craving as a rationale for investigating brain activity linked to drug cue exposure (with many papers containing the word 'craving' in the title or as a keyword). Similarly, studies have routinely interpreted and discussed the implications of their findings in relation to craving. Thus, we believe it is reasonable to assert that neuroimaging cue–reactivity studies have generally sought to induce clinically relevant states of craving; but what exactly constitutes clinically relevant craving?

Our first point is that craving at its core represents not just a desire to use drugs but rather a *strong* desire to do so [2,7,8]. To find support for this idea, one need look no further than the descriptions of craving offered by internationally recognized leaders in the field of addiction research. Consider the following quotation from a recent review by Volkow and colleagues [8]:

> Some of the most pernicious features of drug addiction are the overwhelming craving to take drugs that can reemerge even after years of abstinence, and the severely compromised ability of addicted individuals to inhibit drug seeking once the craving erupts in spite of well-known negative consequences (p. 753).

This portrayal of craving as an overpowering experience is consistent with the notion that the desire to use drugs takes on particular clinical significance when it reaches an intense level [2,9]. The following depiction provided by George & Koob [7] similarly underscores the idea that craving is a state of strong desire:

> Craving is what makes addiction to drugs so difficult to overcome. The intense craving that follows a cue that has been previously associated with the drug, combined with a stressful state or a dysphoric state, represents an unstoppable force that leads to drug intake and relapse for most addicted individuals (p. 4165).

The emphasis on the penetrating nature of craving is also reflected in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM–5; [10]). Craving, which was added as a key symptom of addictive disorders, is defined in the DSM-5 as an 'intense desire or urge', with the manual noting that craving should be assessed by 'asking [individuals] if there has ever been a time when they had such strong urges to use the drug that they could not think of anything else' (p. 483). As noted elsewhere [11], for most individuals addicted to drugs, 'a "weak craving" is an oxymoron' (p. 11). Clearly, then, from both conceptual and clinical perspectives, the focus is on craving as a robust state and not a period of weak to moderate desire.

SUCCESS AT PROVOKING CRAVING HAS VARIED WIDELY ACROSS STUDIES

We believe that many addiction researchers would agree with our first point. It is therefore noteworthy that many neuroimaging cue–reactivity studies have been designed explicitly in a way that minimizes the ability to provoke powerful desires (cravings). To illustrate this point, we conducted a review of fMRI studies in which cigarette cues were presented in an attempt to elicit a desire to smoke in adults. We identified studies by searching the Medline/Pubmed database using a combination of keywords related to smoking/craving (cigarette, craving, cue, desire, smoker, smoking, or urge) and fMRI (blood-oxygen-level dependent, BOLD, brain imaging, fMRI, imaging, MRI, or neuroimaging). Of the identified studies, we included those for which peak self-reported urge, expressed as a percentage of the maximum scale value, could be discerned (those reporting only baseline urge levels, only changes in urge or failing to report scale end-points were excluded), yielding a total of 32 (sub)samples across 24 studies (several studies included multiple subgroups and/or conditions; see Table 1).

As presented in Table 1, 12 of the 32 samples instructed participants to smoke *ad libitum* before the

Table 1 Means [standard deviation (SD)] for select sample characteristics.

First author	*Year*	*Subgroup and/or condition*	*Cue(s)*	*Urge measure*	*% of scale*
Nicotine-deprived					
Canterberry	2013	Prior to neurofeedback	Pic	1–10 scale	64
David	2005	NA	Pic	SJCS	50
David	2007	First abstinent session	Pic	SJCS	57
David	2007	Second abstinent session	Pic	SJCS	76
Due	2002	NA	Pic	0–6 scale	84
Goudriaan	2010	Heavy smokers	Pic	QSU (partial[c])	59
Kober[a]	2010	Focusing on immediate effects of smoking	Pic	1–5 scale	85
Li	2013	Not resisting urge	Pic; handle	1–5 scale	73
McBride[a]	2006	Expectant group; abstinent session	Vid	QSU (partial[b])	70
McBride[a]	2006	Non-expectant group; abstinent session	Pic	QSU (partial[b])	75
McClernon[a]	2005	Abstinent session	Pic	SJCS	69
Stippekohl	2010	Abstinent group; images of 2nd smoking stage	Pic	1–9 scale	74
Westbrook	2011	Responding naturally	Pic	1–5 scale	56
Wilson	2005	Expectant group	Handle	0–100 scale	72
Wilson	2005	Non-expectant group	Handle	0–100 scale	77
Wilson	2012	Quitting-unmotivated; expectant group	Handle	0–100 scale	75
Wilson	2012	Quitting-unmotivated; non-expectant group	Handle	0–100 scale	73
Wilson	2012	Quitting-motivated; expectant group	Handle	0–100 scale	77
Wilson	2012	Quitting-motivated; non-expectant group	Handle	0–100 scale	70
Xu	2012	Weighted mean of high and low urge groups	Pic	0–100 scale	50
					Mean = 69.3, SD = 10.1
Non-deprived					
Bourque	2013	NA	Pic	0–100 scale	47
Brody	2007	Not resisting urge	Vid	1–5 scale	58
Culbertson	2011	Placebo group; pre-treatment; not resisting urge	Vid	1–5 scale	61
David	2007	First non-abstinent session	Pic	SJCS	31
David	2007	Second non-abstinent session	Pic	SJCS	36
Franklin	2007	NA	Vid; handle	1–7 scale	69
McBride[a]	2006	Expectant group; non-abstinent session	Vid	QSU (partial[b])	50
McBride[a]	2006	Non-expectant group; non-abstinent session	Vid	QSU (partial[b])	62
McClernon[a]	2005	Non-abstinent session	Pic	SJCS	50
Smolka	2006	NA	Pic	0–100 scale	49
Stippekohl	2010	Non-abstinent group; images of 2nd smoking stage	Pic	1–9 scale	52
Vollstädt-Klein	2011	NA	Pic	0–100 scale	41
					Mean = 50.5, SD = 11.0

Handle = holding and viewing an unlit cigarette; QSU = Questionnaire on Smoking Urges; Pic = viewing smoking-related pictures; SJCS = Shiffman–Jarvik Craving Scale; Vid = viewing smoking-related videos. [a]Urge scores were estimated from a figure. [b]Participants completed a subset of seven items selected from the QSU. [c]Participants completed subset of 10 items selected from the QSU (it is unclear whether this was the 10-item version of the QSU referred to as the QSU-brief).

experiment [12–21], while the remaining 20 required participants to abstain from smoking for a period of time (ranging from 2–16 hours) prior to the onset of the experimental visit(s) [15,17,18,20,22–31]. As expected, mean ratings of the desire to smoke were noticeably larger in nicotine-deprived smokers (69.3% of scale maximum) relative to non-deprived smokers (50.5% of scale maximum). The difference in average smoking desire is even more striking when considering the proportion of nicotine-deprived versus non-deprived samples for which mean ratings fell above or below the mid-point of the scale. As shown in Fig. 1, mean ratings fell in the upper half of the scale for almost all (90%) nicotine-deprived samples, but only a minority (42%) of the non-deprived samples.

In some cases [15,17,18], studies measured responses in smokers under both non-deprived and deprived conditions with the goal of directly examining potential differences in brain activation between these states. Nevertheless, we argue that the field has generally not paid sufficient attention to the fact that many previous studies have used procedures that dampen cravings. For instance, results obtained from addicted individuals in non-deprived and deprived states are often lumped

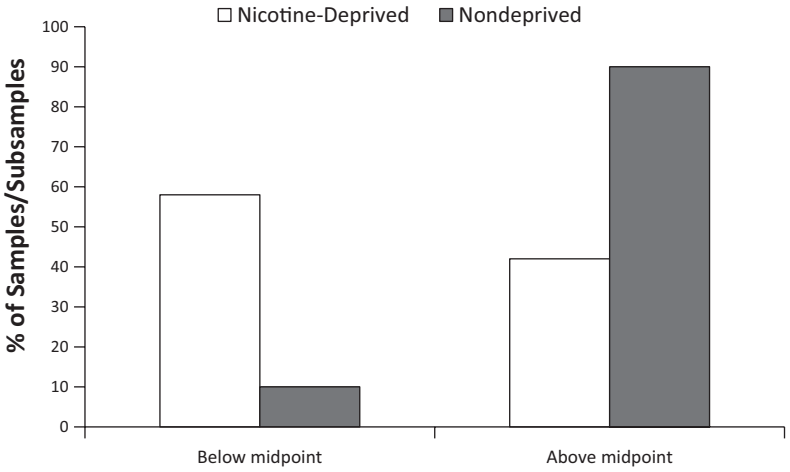

Figure 1 The percentage of samples of nicotine-deprived (white bars) and non-deprived (gray bars) smokers for which mean self-reported urge ratings fell above or below the mid-point of the urge rating scale

together with relatively little consideration of the very different conditions under which such results were obtained (but see [4]). Indeed, we have done so ourselves in prior work [3]. This overlooks what we believe is a crucial point. Namely, for some studies—especially those requiring periods of nicotine deprivation—brain responses to cigarette cues have been measured in the context of a strong desire/craving to smoke (akin to what was described by Drs Volkow, Koob, and their colleagues [7,8], and that is featured in DSM-5 [10]). For many other studies, however, cue-elicited brain activity has been assessed in smokers experiencing a more modest desire to smoke. Moreover, we suspect that this remains an ongoing issue for the field (i.e. that additional brain imaging studies using suboptimal procedures for provoking craving are being conducted).

STUDYING MILD DESIRE MAY NOT BE THE SAME AS STUDYING CRAVING

The patterns presented in Fig. 1 are of little consequence if there are only quantitative differences between the responses measured during mild versus strong desires/cravings. To the contrary, there are reasons to challenge this notion on both conceptual and empirical grounds. From a conceptual perspective, there would seem to be a clear distinction between how drug cues are processed by addicts during a modest desire to consume drugs—such as immediately following substance use—relative to those in the midst of an intense desire that is fueled in part by acute abstinence [15–18]. The idea that there is a qualitative difference between desires of high and low intensity is compatible with basic theory and research regarding the nature of emotional experiences [32]. To the extent that affect is an important component of the desire to use drugs [32], such desire states may be expected to change qualitatively or non-linearly and take on unique properties as they become particularly robust (see [9]).

In line with this view, Sayette and colleagues found that disparate measures of cigarette craving converge on a single common factor only at high levels of desire created through the combination of nicotine deprivation and smoking cue exposure; craving measures did not covary at comparatively weak levels of desire (i.e. in non-deprived smokers exposed to smoking cues) [33]. Similarly, Gwaltney *et al.* observed that quitting smokers exhibited a significant drop in their confidence to remain abstinent from smoking only during maximal urge states [34]. Abstinence, self-efficacy and craving were not associated when smoking desire was not at its peak, suggesting that cravings may be a categorically different experience from less potent states of desire. Collectively, such research indicates that conclusions may be limited in studies that measure cue-elicited brain activity in those whose desire to smoke has recently been satisfied. For instance, unlike nicotine-deprived smokers in a state of craving, non-deprived smokers with low levels of desire may not be especially useful for characterizing the appetitive motivational responses that contribute to relapse in those trying to quit smoking [32].

Pertinent to this issue, Engelmann and colleagues [4] recently compared the responses of four studies of nicotine-deprived smokers to eight studies of non-deprived smokers. Although craving was not a focus of their review and the number of studies was small, the authors nevertheless found that cue exposure was associated more reliably with increases in activation of the inferior occipital cortex and superior frontal gyrus in nicotine-derived than non-deprived smokers. Results also suggested that smoking cues were associated with the activation of a larger extent of the prefrontal cortex (PFC) in nicotine-deprived relative to non-deprived smokers, although this pattern was not significant in a formal subtraction analysis. These findings reinforce the idea that smoking satiety influences brain responses to cigarette cues, perhaps because of differences in the level of

Table 2 Studies included in activation likelihood estimation meta-analysis.

First author	*Year*	*Contrast*	*Cue(s)*	*n*	*Foci*
Nicotine-deprived					
Claus	2013	Cig > Food-related	Vid	116	11
David	2005	Cig > Neu	Pic	9	3
David	2007	Cig > Neu (abstinent session)	Pic	8	2
Goudriaan	2010	Cig – Neu (high FTND smokers > non-smokers)	Pic	10	7
Hartwell	2011	Cig > Neu (not resisting urge)	Pic	31	12
Kang	2012	Cig > Neu	Pic	25	17
Li	2013	Cig > Rest (not resisting urge)	Pic; handle	10	10
McClernon	2009	Cig > Neu (abstinent session)	Pic	18	19
Westbrook	2011	Cig > Neu (responding naturally)	Pic	47	2
Wilson	2005	Cig > Neu	Handle	20	9
Wilson	2012	Cig > Neu	Handle	90	12
Zhang	2011	Cig – Neu (smokers > non-smokers)	Pic	22	6
Non-deprived					
Bourque	2013	Cig > Neu	Pic	31	5
Brody	2007	Cig > Neu (not resisting urge)	Vid	42	17
Dagher	2009	Cig > Neu (no stress condition)	Vid	15	3
David	2007	Cig > Neu (non-abstinent session)	Pic	8	2
Diggs	2013	Cig > Neu	Pic	9	1
Franklin	2009	Cig > Neu (9 repeats)	Vid; handle	10	9
Franklin	2009	Cig > Neu (10/10 repeats)	Vid; handle	9	13
Franklin	2011	Cig > Neu	Vid	26	1
Janes	2009	Cig > Neu (pre-treatment scan)	Pic	13	25
Janes	2012	Cig > Neu	Pic	24	11
McBride	2006	Cig > Neu (non-abstinent session)	Vid	19	5
Versace	2011	Cig > Neu	Pic	35	13
Vollstädt-Klein	2010	Cig > Neu	Pic	22	13
Yalachkov	2009	Cig – Neu (smokers > non-smokers)	Pic	15	12

Cig = cigarette-related cues; FTND = Fagerström Test for Nicotine Dependence; Handle = holding and viewing an unlit cigarette; Neu = neutral cues; Pic = viewing smoking-related pictures; Vid = viewing smoking-related videos.

smoking desire experienced by nicotine-deprived and non-deprived smokers. The small number of smoking studies reviewed limited the ability to draw conclusions, however, especially in light of relevant studies that were omitted. (Because this review focused on cue-specific reactivity rather than craving *per se*, it excluded research in which participants reported some of the most robust cravings [29].)

Given these constraints, we conducted a meta-analysis of fMRI studies of smoking cue-elicited craving using activation likelihood estimation (ALE) [35], as implemented with GingerALE version 2.3 (http://www.brainmap.org). This provided an opportunity to more than double the number of studies reviewed by Engelmann and colleagues [4]. Studies were identified using the same search strategy described above. We included all available fMRI studies that assessed cue–reactivity in adult smokers, conducted whole-brain analyses and reported coordinates in Montreal Neurological Institute (MNI) or Talairach space (with Talairach coordinates converted to MNI) for regions exhibiting significant cue-related increases in activation. Like Engelmann *et al.* [4], we excluded studies in which participants were instructed to inhibit or cope with craving or were taking smoking-cessation medications at the time of scanning (unless the study also reported results for a pre-treatment scan or a condition in which participants were instructed not to resist craving), and those in which smoking cues were presented in the background or periphery while participants performed a separate task.

We identified 26 (sub)samples meeting these criteria (see Table 2): 12 from studies that required participants to abstain from smoking for a period of time before the experiment [15,23,25,27–30,36–40] and 14 from studies that instructed participants to smoke *ad libitum* prior to the scan session [12,13,15,17,21,41–48]. (Note that David *et al.* [15] included both nicotine-deprived and non-deprived samples and that this set of studies only partially overlaps with those included in the analysis of peak craving described above. In addition, our classification of one study differed from that of Engelmann and colleagues [4]. Specifically, we included the report by Hartwell *et al.* [37] among the studies of deprived

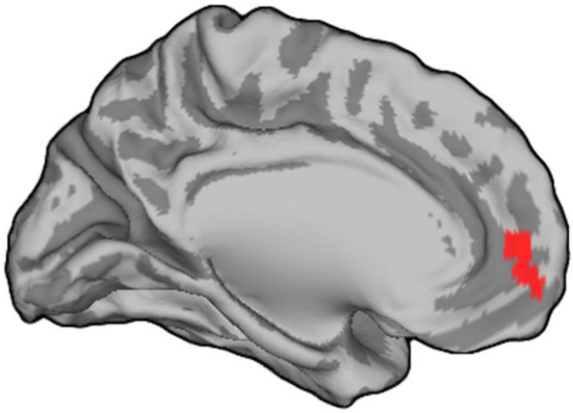

Figure 2 Region of the rostral anterior cingulate cortex (ACC) and adjacent medial/ventromedial prefrontal cortex (PFC) (depicted in red) more reliably activated by cigarette cues in nicotine-deprived than non-deprived smokers, as indicated by activation likelihood estimation (ALE) subtraction analysis

smokers, as participants were instructed to abstain from smoking for 2 hours prior to the experiment.)

Our meta-analysis revealed that smoking cues have been associated with activation of a larger portion of the rostral anterior cingulate cortex (rACC) in nicotine-deprived smokers (4360 mm^3) relative to non-deprived smokers (1184 mm^3) when each was considered separately. In order to evaluate more directly the significance of this pattern, we conducted a subtraction analysis [35] contrasting the ALE maps generated for studies of nicotine-deprived versus non-deprived smokers. Results confirmed that a region encompassing the rACC and adjacent medial/ventromedial PFC (MNI coordinates $x = -9$, $y = 49$, $z = -8$; size = 960 mm^3, Brodmann's areas 32 and 10) was more likely to exhibit increased activation during cigarette cue exposure in the nicotine-deprived samples ($P < 0.05$ false discovery rate corrected, with a minimum cluster size of 200 mm^3; see Fig. 2). This difference is notable in light of emerging research highlighting the importance of the rACC in relation to the treatment of craving and the regulation of affect, more generally [1,8,13,14,22,27,37]. There were no regions more reliably activated by cigarette cues in non-deprived relative to deprived smokers.

We hypothesize that this differential engagement of the rACC was driven, at least in part, by differences in the degree to which nicotine-deprived versus non-deprived smokers experienced the desire to smoke. Although it was impossible to test this idea directly because peak ratings of smoking desire were not available for most studies, indirect support comes from research examining the neurobiological effects associated with interventions designed to reduce craving. In one line of research, Brody and colleagues have demonstrated that treatment with bupropion hydrochloride—a medication that reduces both background and cue-provoked craving—attenuates activation of the rACC by cigarette cues in smokers (e.g. [14]). In a second line of work, Brady, George and colleagues have shown that smokers can be taught to decrease cue-elicited activation of the rACC using real-time fMRI neurofeedback and that so doing is associated with reductions in urge [22,27]. Thus, manipulations that weaken the desire to use drugs appear to reduce activation of the rACC during cue exposure.

Results from our meta-analysis are thus consistent with the idea that non-deprived smokers exhibit less reliable activation of the rACC because the desire to smoke is relatively modest when cues are paired with cigarette satiety, whereas the combination of deprivation and salient cigarette cues produce particularly robust desire/craving. More generally, we propose that, as with behavioral studies [8], it is possible—perhaps even likely—that neuroimaging studies assessing smokers in a modest state of desire (such as immediately following smoking) and those assessing smokers in the midst of a relatively powerful craving episode are, to some degree, measuring distinct concepts.

Furthermore, the differential activation of the rACC identified in our meta-analysis may represent only the tip of the iceberg regarding how neurobiological responses to smoking cues are shaped by urge intensity. As has been noted [30], it is the spatiotemporal relationships (i.e. connectivity) between brain regions, and not differences in the mean activation level within brain regions in isolation, that may best elucidate the nature of cue-elicited neural responses. Of particular relevance, our prior work suggests that connectivity between the rACC and other areas of the brain is especially sensitive to the motivational context associated with smoking cue exposure (e.g. smoking expectancy) [30]. Hence, while the potential link between the strength of cravings and cue-elicited activation of the rACC itself has salient conceptual and clinical implications, we anticipate that the importance of craving intensity will become even clearer as the assessment of brain connectivity during urge states becomes more widespread.

GREATER ATTENTION TO URGE INTENSITY WOULD HELP TO ADVANCE THE FIELD

We believe that more explicit attention to urge intensity in addiction neuroimaging research has the potential to yield valuable information about craving. Among many fruitful avenues for future research, the application of imaging to tightly manipulated levels of craving may be particularly effective for clarifying whether craving manifests as a linear or non-linear phenomenon—a fundamental issue that remains unresolved within the field

[9,49,50]. Neuroimaging could be used to assess changes in the strength of the desire to use drugs from low to very high (e.g. as produced by manipulating the duration of nicotine deprivation and intensity of cue exposure) in relation to both the magnitude of activation within localized brain regions and patterns of connectivity among brain areas. Such research may reveal, for example, that changes in drug use desire are associated with corresponding adjustments in the magnitude of activation and/or connectivity within some relatively fixed set of brain areas (a 'craving network'), suggesting that craving is best conceived of as linear. Alternatively, increases in desire above some threshold may result in the emergence of new brain areas/connections (e.g. brain responses linked to motivation and action preparation appearing only after desire is very high), suggesting that craving may be non-linear. Neuroimaging methods are uniquely well suited for distinguishing between these and other possibilities (e.g. some combination of linearity and non-linearity) regarding the nature of craving. Relatedly, research is needed to directly examine the extent to which urge intensity moderates the association between cue-elicited brain responses and clinically relevant outcomes such as relapse. Although, in some instances, nicotine-deprived smokers' baseline urges and their 'peak' urges following smoking cue exposure are similarly linked to subsequent relapse (see [9]), it may be that the neural responses during intense desire associated with nicotine-deprived states ultimately prove to be more strongly associated with clinical outcomes than are responses during non-deprived states. This possibility requires experimental verification, as some work suggests that lighter states of desire may offer a sensitive predictor of relapse (see [50]).

More generally, we believe that a greater focus on the intensity of substance use desires in neuroimaging research would benefit the field even if such work ultimately reveals that craving intensity has only modest effects on neurobiological responses to drug cues, as it would challenge the widespread argument that there is something unique about strong desires. Models of addiction and craving would require critical revisions in order to accommodate such an unexpected result. Regardless of the outcomes of future studies, however, our point of emphasis is that advancing knowledge regarding the neurobiology of craving requires deeper consideration of just how we manipulate and assess craving.

SUMMARY AND CONCLUSIONS

Functional neuroimaging research on craving for cigarettes and other drugs has come a long way in a remarkably short period of time. The field has generally moved beyond a focus on 'mapping' brain responses to drug-related cues and is becoming dominated by studies attempting to address increasingly nuanced questions about urges. Collectively, this research has led to some of the most exciting advances in the study of addiction [1,8]. As a field, however, we have not paid sufficient attention to the very phenomenon under study. Namely, in many studies purporting to examine craving, participants endorse only a weak desire to use drugs, while in others participants endorse exceptionally strong desires. It is notable that the actual amount of craving reported by participants is not given much consideration in many imaging smoking cue–reactivity studies. Indeed, one wonders what it means to talk about the 'neural correlates of craving' in smokers reporting mild urges that seemingly fall far short of the powerful state that is believed to be important from both theoretical [2,7,8] and clinical/diagnostic [10] perspectives.

We believe that it is important to pay close attention to the intensity of the cravings that one is studying, regardless of the research tools that are utilized and types of responses that are measured. We have emphasized functional brain imaging because it has become an especially prevalent and influential approach to studying craving—and because neuroimaging methods present distinct challenges when it comes to manipulating and measuring craving (e.g. the fMRI environment is noisy and cramped and generally precludes the use of certain highly potent drug cues, such as a burning cigarette)—but we believe that our claims apply whether one is assessing brain activity or other response modalities (for additional discussion, see [9]). Regarding functional brain imaging methods specifically, it is useful to keep in mind that by themselves the data they provide are merely indicators of changes in electrophysiological (e.g. as measured using electroencephalography) or hemodynamic (e.g. as measured using fMRI) activity in the brain. In order to derive meaningful insights from such data, they must be considered in the context of the study manipulations and other measures (see [49]). Urge intensity represents one such variable.

We have highlighted acute nicotine deprivation as a factor that affects the desire to smoke, and thus as a useful factor for parsing studies, but our more fundamental point is that craving intensity itself warrants greater attention. We recognize that there are several other relevant factors worth considering (e.g. robustness of the cues that are used to elicit craving [9], perceived opportunity to smoke during the study [30]). Additionally, we did not address the possibility that drug withdrawal has effects on responses (including those measured in the brain) that are separate from those it has on craving, as we viewed this issue to be beyond the scope of our argument. Nonetheless, research exploring whether the effects of drug deprivation and craving can be

disentangled would be useful (e.g. see [16]). In reviewing peak urge ratings reported in previous studies, we necessarily collapsed across studies using different craving scales. The assumption is that the different end-points of these scales do not affect how respondents use them, which may or may not be accurate. Finally, while we have concentrated on craving for cigarettes, we believe that the intensity of subjective experience also may be critical when studying craving for other drugs.

Notwithstanding these caveats, we believe that the points made herein have significant implications for research in which tools from neuroscience are used with the goal of examining drug craving. Simply put, studying brain responses during mild desires may not be the same as studying brain responses during overpowering urges. Therefore, inconsistency in urge intensity should be taken into account as a potentially important source of heterogeneity across prior studies. In addition, by focusing more on urge intensity in future work, addiction researchers have the potential to provide novel insight into some of the most pressing questions concerning the construct of craving itself.

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Declaration of interests

None.

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