individual has difficulty thinking about anything else could approximate loss of control over substance use [2]. Working within cue–reactivity studies among cigarette smokers, the authors conducted a meta-analysis exploring differences in reported craving and brain activation among smokers who had been deprived before scanning and those who had smoked a cigarette just before participation. They observed significantly lower urge ratings among non-deprived participants, and found a region of the anterior cingulate cortex (ACC) extending into the ventromedial prefrontal cortex (PFC) thatwas more likely to show increased activation during cigarette cues in deprived than in non-deprived smokers. The authors use this finding to highlight the importance of carefully considering craving intensity when interpreting cue–reactivity studies.

The ACC has been implicated as a node between regions related to reward (i.e. subcortical regions project to the ACC) and cognitive control (i.e. the ACC projects to the PFC). The likely mechanism is that reward response activates the ACC which, in turn, activates PFC to initiate planning and appetitive behavior [3]. Overall, the increased likelihood of greater activation in ACC/PFC observed by the authors is consistent with increased craving among deprived smokers. However, a major potential confound identified by Sayette & Wilson [1] should be considered in more detail. In the included studies, deprived smokers had abstained for 2–16 hours, and non-deprived smokers had been instructed to smoke as they desired. The effects of nicotine may last for hours after the last smoked cigarette, and nicotine is notably associated with vasoconstriction [4]. It is therefore still difficult to interpret blood oxygen level-dependent signals in deprived smokers, given the variance in time since the last cigarette was smoked. Time since last cigarette and/or a measure of urgency of craving should, arguably, be included as a covariate in functional analyses.

Studies among non-deprived smokers may still be useful in understanding relapse prevention. Decreased ACC activation during a modest desire to smoke, or when a craving has presumably been satisfied, provides additional support for reduced activation of the ACC as a biomarker for decreased craving and a possible predictor of treatment efficacy. Further treatment development could approach smoking cessation by reducing reward or by increasing cognitive control. Given that the authors excluded any studies where participants were instructed to resist craving or to attempt to reduce urges to use, additional studies could compare activation in those attempting to control their craving, those who recently satisfied their craving and those who were experiencing intense craving. Such a study could inform clinical conceptualization of craving (e.g. linear or nonlinear intensity with varying cognitive processes). It could also elucidate whether intense craving is an entirely distinct construct involving recruitment of additional functional regions, or any regions of decreased activation (e.g. in additional cognitive control circuitry), compared to more modest desire or satisfied urge.

Despite potential limitations, imaging measures provide an important link between behavioral approaches to treatment and changes in the brain that may underlie treatment gains. Future studies will probably incorporate multi-modal imaging or multiple analytical techniques. Further consideration of construct validity in functional neuroimaging studies will be important in increasing translational impact in improving treatment efficacy, as well as increasing the ability of researchers to compare results meaningfully across studies.

### Declaration of interests

None.

**Keywords** Addiction, anterior cingulate, craving, neuroimaging, prefrontal cortex, treatment.

RACHEL E. THAYER & BARBARA J. WEILAND
*Department of Psychology and Neuroscience, University of Colorado Boulder, Boulder, CO 80309-0345, USA.*
*E-mail: rachel.thayer@colorado.edu*

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## ALL CRAVINGS ARE NOT CREATED EQUAL

In our paper, we argued that it is important to consider urge intensity when examining the neural correlates of craving [1] because we believed that there were important conceptual and empirical reasons for this position (illustrated empirically by differences between deprived and non-deprived samples). We noted that researchers have often ignored the potential significance of urge levels, so we were gratified to see that the commentators generally seemed comfortable with what we thought might be viewed as a controversial critique [2–3]. We hope that, moving forward, researchers conducting 'craving' studies

with non-deprived smokers will address whether their findings may relate to less intense states of desire.

Moeller *et al.* [2] suggest that the concept of craving requires refinement. They propose additional factors besides deprivation that might distinguish between 'low-level desire and clinically-relevant craving'. We agree that deprivation is just one factor relevant to urge intensity that warrants increased attention [4], and that its role in craving varies across drugs of abuse. We also concur that improved assessment of craving is needed in neuroimaging research, although we note that it may be difficult to do so in a multi-trial design because of the likely protracted duration of robust craving responses and potential carry-over effects [5,6].

Potvin found 'inspiring' our central point that urge intensity matters. Nonetheless he requested additional data to address potential overlapping activation between studies of deprived and non-deprived smokers that we provide in supplementary tables. Deprived and non-deprived samples yielded largely divergent activation patterns, with only three of 22 foci identified as overlapping across study types. Although we observed some overlap in the rostral anterior cingulate cortex (rACC), the overlapping portion was significantly smaller than the region exhibiting more reliable activation for deprived versus non-deprived studies (240 versus 960 $mm^2$, respectively). We hope that these new data, and the observation that cue exposure generates more reliable activation across a much larger portion of the rACC in deprived groups, provides more persuasive evidence for our hypothesis that uncontrollable and moderate cravings may trigger different brain responses. This is supported by recent work linking the rACC to clinically relevant reductions in craving [7–12].

We agree with Thayer & Weiland [3] that there still may be value to studying smokers experiencing mild desire. Ultimately, decisions regarding experimental design should be guided by theory and the specific goals of the study. Like Thayer & Weiland, we believe that our understanding of addiction will benefit not only from studying brain responses during states of intense desire (craving), but also by examining brain activity when this desire is satisfied (e.g. [13]) or actively inhibited (e.g. [14]). As they note, addressing the potential influence of acute nicotine (and nicotine withdrawal, for that matter) on hemodynamics and neurovascular coupling is also warranted, although these effects may be complex (e.g. [15]).

In sum, we agree with all the commentators that there may well be a host of variables that influence the neural correlates of craving. We hope that this set of papers and commentaries reinforces the view that not all cravings are equivalent, that there is a need for clearer focus on how craving is conceptualized, manipulated and measured, and more recognition that deprivation level is a particularly important variable to consider.

**Keywords** craving, cue exposure, cue reactivity, deprivation, fMRI neuroscience.

STEPHEN J. WILSON[1] & MICHAEL A. SAYETTE[2]
*The Pennsylvania State University and the Center for Brain, Behavior and Cognition, University Park PA, USA*[1]
*and University of Pittsburgh and the Center for the Neural Basis of Cognition, Pittsburgh, PA, USA*[2]
*E-mail: sjw42@psu.edu*

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