Invited Review

Multisensory Environments to Measure Craving During Functional Magnetic Resonance Imaging

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Abstract

There are limited functional magnetic resonance imaging (fMRI) studies that measure alcohol craving with multisensory environments. Researchers are faced with a two-fold challenge: to recreate a naturalistic environment during an MRI scan and to produce paradigms that mimic real-life conditions involved with craving. Craving is a multifaceted psychological construct and techniques such as fMRI provide an alternative way to measure craving and to have a better understanding of its complexity. Most studies to date have implemented visual stimuli to measure craving and only a few studies have investigated gustation and olfaction. Moving forward, there needs to be greater attention on the ways in which we measure craving and the use of multisensory environments during fMRI. By going beyond examining subjective craving responses, and investigating neurobiological responses such as brain activity during fMRI, can potentially lead to better treatments for alcohol use disorder. Further, there needs to be additional consideration on standardizing how we measure craving, which will allow for a more unified approach amongst researchers.

Neuroimaging researchers face a major challenge in recreating a naturalistic environment during a functional magnetic resonance imaging (fMRI) scan. During an MRI scan, participants are placed laying down in a narrow tube with a head coil covering their head. Further complicating the issue for researchers is to create paradigms that evoke brain activity in participants that mirror real-life activities. What is missing in a cold and sterile MRI room is a multisensory environment that people experience in the real world. For instance, a wine aficionado would first smell the wine, swirl the contents in a glass and then sip it gradually. Similarly, a smoker walking down the street would then have an urge to smoke after seeing and smelling cigarette smoke. There would be an overall experience involved with cue-elicited craving.

Craving is a psychological construct that is often defined as a strong desire or urge to use or consume a substance and has recently been added as new criteria in the 5th edition of the Diagnostic and

Statistical Manual of Mental Disorders (DSM-5; [First et al., 2014](#)). There has been over twenty years of research investigating alcohol craving in the addiction field ([Anton, 1999](#); [Rohsenow and Monti, 1999](#)) and, over the years, many research groups have created bar-like laboratory settings to create naturalistic conditions for participants ([Leggio et al., 2015](#); [Haass-Koffler et al., 2018](#)). Despite the wealth of literature on subjective craving for alcohol ([Cooney et al., 1997](#); [Tiffany and Conklin, 2000](#); [Haass-Koffler et al., 2014](#)), cigarettes ([Carter and Tiffany, 2001](#); [Drobes, 2002](#)) and other substances ([Fatseas et al., 2011](#); [McRae-Clark et al., 2011](#)), the psychological constructs and biological influences of craving are not adequately understood. Furthermore, while self-report in behavioral studies may provide useful information, these assessments/instruments can be subject to biases and inaccuracies ([Kavanagh et al., 2013](#)). Therefore, techniques such as fMRI can provide a more objective metric to measure the neurobiological mechanisms to better characterize

the complexity and multidimensionality of craving. Furthermore, fMRI approaches may provide insight into treatment responses for alcohol use disorder (Heilig and Leggio, 2016). For example, a key biomarker in addiction is mesolimbic dopamine (DA) transmission and it has been shown that DA released in the nucleus accumbens leads to increased blood oxygen-level dependent (BOLD) signal (Knutson and Gibbs, 2007). Thus, BOLD fMRI signals can be a potential biomarker of alcohol-induced DA activation.

Currently, there are limited MRI-compatible methods for exposing participants to alcohol cues in a scanner in a way that is comparable to how participants are exposed to these cues in behavioral studies (i.e. seeing, touching and smelling alcohol in a laboratory). Most fMRI studies rely on pictures as the primary form of stimuli since other methods (e.g. delivering alcohol vapors) are more costly and burdensome to implement. As a result, there are limited fMRI studies with multisensory environments. Furthermore, with different modalities come different ways to measure craving, which inherently will not all produce the same results. The variability in how craving is measured across studies limits the ability to replicate findings and to have a unified approach for assessing craving.

One way to create a more realistic environment during an fMRI scan is to provide participants with small sips or drops of alcohol. A few fMRI studies have investigated alcohol craving during alcohol gustatory tasks (Filbey *et al.*, 2008; Courtney *et al.*, 2015) and with the combination of gustatory and visual cues (George *et al.*, 2001; Myrick *et al.*, 2010).

These studies provide evidence that there are behavioral and neural responses to alcohol craving associated with alcohol priming. However, each study found distinct activation patterns due to differences such as sample characteristics (e.g. genotyping) and exposure to alcohol (e.g. pre- and post-scan). Further, craving may be mitigated after a participant tastes alcohol and it could be argued that the baseline for craving is higher after even a little bit of alcohol is consumed.

In addition to visual and gustatory stimuli, olfactory cues are another beneficial way of inducing alcohol craving. Olfactory nerves (i.e. those stimulated by olfactory cues) synapse in limbic brain regions and may play a large role in cue-elicited craving (Schneider *et al.*, 2001; Lowen *et al.*, 2017). This finding is supported by pre-clinical studies that have shown that ethanol olfactory stimuli can cause reinstatement of alcohol-seeking behaviors after extinction (Katner and Weiss, 1999) and experiences with alcohol odors can affect alcohol preferences and consumption (Bierut *et al.*, 2010). Only a few studies have investigated olfactory alcohol cues (Kareken *et al.*, 2004; Bragulat *et al.*, 2008; Lukas *et al.*, 2013) and their impact on craving. Similar to the alcohol gustatory findings, these studies also show behavioral responses and activation patterns in response to alcohol olfactory cues. However, each alcohol olfactory study showed different neural responses to craving due to methodological differences (e.g. medications taken by participants, alcohol priming, etc.). Furthermore, fMRI studies investigating olfactory cigarette (Cortese *et al.*, 2015) and marijuana (Frederick *et al.*, 2007) cues have demonstrated that odors play an important role for understanding cue-elicited craving. Therefore, olfactory cues can be useful for investigating craving for other drugs of abuse (e.g. nicotine, cannabis).

To date, there is a lack of fMRI studies assessing craving with multisensory environments and most studies have used pictures as the primary form of stimuli. Understandably, implementing multiple

cues can be costly and difficult to carry out for most researchers. In addition, there is a lack of understanding of what encompasses craving. Are we doing enough to capture all of the components of craving? By investigating craving elicited by cues are we only investigating one dimension? Craving can occur before one sees, smells or tastes a substance. A further difficulty for researchers is measuring craving during an fMRI scan. Participants need to be exposed to some sort of stimuli and our current method for measuring craving may not fully encapsulate what we intend to measure.

Taken together, more attention is needed for identifying different components of craving. These components need to encompass not only subjective responses, but also a multitude of different factors such as biological mechanisms. Researchers should be encouraged to share equipment and paradigms to help implement multisensory environments. Lastly, there needs to be further consideration about a standardized way to measure craving to limit variability across studies and to enable others to replicate work and findings. A cohesive approach and understanding of craving will enable researchers to have a better comprehension of one important element of addiction.

SUMMARY

Recreating multisensory environments during functional magnetic resonance imaging (fMRI) remain a challenge for most researchers. To fully understand the multifaceted components of alcohol craving, more effort is needed to create fMRI paradigms with multisensory cues (e.g., sight, smell and taste of alcohol) to mimic real-life conditions.

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CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

- Anton RF. (1999) What is craving? Models and implications for treatment. *Alcohol Res Health* 23:165–73.
- Bierut LJ, Agrawal A, Bucholz KK, *et al.* (2010) A genome-wide association study of alcohol dependence. *Proc Natl Acad Sci USA* 107:5082–7. doi:10.1073/pnas.0911109107.
- Bragulat V, Dziedzic M, Talavage T, *et al.* (2008) Alcohol sensitizes cerebral responses to the odors of alcoholic drinks: an fMRI study. *Alcohol Clin Exp Res* 32:1124–34. doi:10.1111/j.1530-0277.2008.00693.x.
- Carter BL, Tiffany ST. (2001) The cue-availability paradigm: the effects of cigarette availability on cue reactivity in smokers. *Exp Clin Psychopharmacol* 9:183–90.
- Cooney NL, Litt MD, Morse PA, *et al.* (1997) Alcohol cue reactivity, negative-mood reactivity, and relapse in treated alcoholic men. *J Abnorm Psychol* 106:243.
- Cortese BM, Uhde TW, Brady KT, *et al.* (2015). The fMRI BOLD response to unisensory and multisensory smoking cues in nicotine-dependent adults. *Psychiatry Res* 234:321–7.
- Courtney KE, Ghahremani DG, Ray LA. (2015) The effect of alcohol priming on neural markers of alcohol cue-reactivity. *Am J Drug Alcohol Abuse* 41:300–8. doi:10.3109/00952990.2015.1044608.

- Drobes DJ. (2002) Cue reactivity in alcohol and tobacco dependence. *Alcohol Clin Exp Res* 26:1928–9. doi:10.1097/01.alc.0000040983.23182.3a.
- Fatseas M, Denis C, Massida Z, *et al.* (2011) Cue-induced reactivity, cortisol response and substance use outcome in treated heroin dependent individuals. *Biol Psychiatry* 70:720–7.
- Filbey FM, Claus E, Audette AR, *et al.* (2008) Exposure to the taste of alcohol elicits activation of the mesocorticolimbic neurocircuitry. *Neuropsychopharmacology* 33:1391–1401. doi:10.1038/sj.npp.1301513.
- First MB, Williams JB, Karg RS, *et al.* (2015) *Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5-CV)*. Arlington, VA: American Psychiatric Association.
- Frederick B, Lindsey KP, Nickerson LD, *et al.* (2007) An MR-compatible device for delivering smoked marijuana during functional imaging. *Pharmacol Biochem Behav* 87:81–9. doi:10.1016/j.pbb.2007.04.006.
- George MS, Anton RF, Bloomer C, *et al.* (2001) Activation of prefrontal cortex and anterior thalamus in alcoholic subjects on exposure to alcohol-specific cues. *Arch Gen Psychiatry* 58:345–52.
- Haass-Koffler CL, Goodyear K, Zywiak WH, *et al.* (2018) Comparing and combining topiramate and aripiprazole on alcohol-related outcomes in a human laboratory study. *Alcohol Alcohol* 53:268–76. doi:10.1093/alc/alx108.
- Haass-Koffler CL, Leggio L, Kenna GA. (2014) Pharmacological approaches to reducing craving in patients with alcohol use disorders. *CNS Drugs* 28: 343–60. doi:10.1007/s40263-014-0149-3.
- Heilig M, Leggio L. (2016) What the alcohol doctor ordered from the neuroscientist: theragnostic biomarkers for personalized treatments. *Prog Brain Res* 224:401–18. doi:10.1016/bs.pbr.2015.07.023.
- Kareken DA, Claus ED, Sabri M, *et al.* (2004) Alcohol-related olfactory cues activate the nucleus accumbens and ventral tegmental area in high-risk drinkers: preliminary findings. *Alcohol Clin Exp Res* 28:550–7.
- Katner SN, Weiss F. (1999) Ethanol-associated olfactory stimuli reinstate ethanol-seeking behavior after extinction and modify extracellular dopamine levels in the nucleus accumbens. *Alcohol Clin Exp Res* 23: 1751–60. doi:10.1111/j.1530-0277.1999.tb04070.x.
- Kavanagh DJ, Statham DJ, Feeney GFX, *et al.* (2013) Measurement of alcohol craving. *Addict Behav* 38:1572–84. doi:http://dx.doi.org/10.1016/j.addbeh.2012.08.004.
- Knutson B, Gibbs SE. (2007) Linking nucleus accumbens dopamine and blood oxygenation. *Psychopharmacology (Berl)* 191:813–22. doi:10.1007/s00213-006-0686-7.
- Leggio L, Zywiak WH, Edwards SM, *et al.* (2015) A preliminary double-blind, placebo-controlled randomized study of baclofen effects in alcoholic smokers. *Psychopharmacology (Berl)* 232:233–43. doi:10.1007/s00213-014-3652-9.
- Lowen SB, Farmer SL, Lukas SE. (2017) Improved low-cost, MR-compatible olfactometer to deliver tobacco smoke odor. *Behav Res Methods* 49: 74–82. doi:10.3758/s13428-016-0709-1.
- Lukas SE, Lowen SB, Lindsey KP, *et al.* (2013) Extended-release naltrexone (XR-NTX) attenuates brain responses to alcohol cues in alcohol-dependent volunteers: a bold fMRI study. *Neuroimage* 78:176–85. doi: http://dx.doi.org/10.1016/j.neuroimage.2013.03.055.
- McRae-Clark AL, Carter RE, Price KL, *et al.* (2011) Stress- and cue-elicited craving and reactivity in marijuana-dependent individuals. *Psychopharmacology (Berl)* 218:49–58.
- Myrick H, Li X, Randall PK, *et al.* (2010) The effect of aripiprazole on cue-induced brain activation and drinking parameters in alcoholics. *J Clin Psychopharmacol* 30:365–72. doi:10.1097/JCP.0b013e3181e75c5f.
- Rohsenow DJ, Monti PM. (1999) Does urge to drink predict relapse after treatment? *Alcohol Res Health* 23:225–32.
- Schneider F, Habel U, Wagner M, *et al.* (2001) Subcortical correlates of craving in recently abstinent alcoholic patients. *Am J Psychiatry* 158: 1075–83. doi:10.1176/appi.ajp.158.7.1075.
- Tiffany ST, Conklin CA. (2000) A cognitive processing model of alcohol craving and compulsive alcohol use. *Addiction* 95:145–53.