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VIEWPOINT

Prediction of craving across studies: A commentary on conceptual and methodological considerations when using data-driven methods

STEPHANIE ANTONS[1,2,3], SARAH W. YIP[4,5], CHERYL M. LACADIE[6], JAVID DADASHKARIMI[7,8], DUSTIN SCHEINOST[6], MATTHIAS BRAND[1,2,3] and MARC N. POTENZA[4,5,9,10,11,12*]

[1] General Psychology: Cognition, Faculty of Computer Science, University of Duisburg-Essen, Duisburg, Germany

[2] Center for Behavioral Addiction Research (CeBAR), Center for Translational Neuro- and Behavioral Sciences, University Hospital Essen, University of Duisburg-Essen, Germany

[3] Erwin L. Hahn Institute for Magnetic Resonance Imaging, Essen, Germany

[4] Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

[5] Child Study Center, Yale University School of Medicine, New Haven, CT, USA

[6] Department of Radiology and Biomedical Imaging, Yale School of Medicine, New Haven, CT, USA

[7] Department of Radiology, Athinoula. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, USA

[8] Department of Radiology, Harvard Medical School, Boston, MA, USA

[9] Department of Neuroscience, Yale University School of Medicine, New Haven, CT, USA

[10] Connecticut Council on Problem Gambling, Wethersfield, CT, USA

[11] Connecticut Mental Health Center, New Haven, CT, USA

[12] Wu Tsai Institute, Yale University, New Haven, CT, USA

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ABSTRACT

Craving is a central feature of substance use disorders and disorders due to addictive behaviors. Considerable research has investigated neural mechanisms involved in the development and processing of craving. Recently, connectome-based predictive modeling, a data-driven method, has been used in four studies aiming to predict craving related to substance use, addictive behaviors, and food. Studies differed in methods, samples, and conceptualizations of craving. Within the commentary we aim to compare, contrast and consolidate findings across studies by considering conceptual and methodological features of the studies. We derive a theoretical model on the functional connectivity-craving relationships across studies.

KEYWORDS

cue-reactivity, urge, fMRI, functional connectivity, machine learning

*Corresponding author.
E-mail: marc.potenza@yale.edu

Craving, intense urges to engage in a behavior, apply importantly to substance and behavioral addictions (Antons, Brand, & Potenza, 2020; Mallorquí-Bagué, Mestre-Bach, & Testa, 2023; Tiffany & Wray, 2012; Vafaie & Kober, 2022). Understanding brain networks underlying craving thus has implications for treatment development.

Previous work has predominantly focused on inference-statistical and theory-driven analytic approaches where *a-priori* defined hypotheses on the activity or connectivity of

specific brain regions and networks hypothetically related to craving were tested. A large meta-analysis on the neural correlates of cue-reactivity and craving (as well as other addiction-related mechanisms) suggests consistent involvement of the reward network (including the ventral striatum, rostral anterior cingulate cortex, and orbitofrontal cortex) (Zilverstand, Huang, Alia-Klein, & Goldstein, 2018). In addition, the analyses show that while cue-reactivity responses might be anchored in the ventral striatum, the neural responses extend to multiple large-scale networks. Similar results were found for behavioral addictions (Antons et al., 2020). Studies suggest craving as being linked to both altered neural activity and resting-state functional connectivity (Zeng, Han, Gao, Sun, & Yuan, 2023; Zilverstand, O'Halloran, & Goldstein, 2018). One recent meta-analysis investigating resting-state functional connectivity, for example, implicates changes within and between the fronto-parietal network, the ventral attention network and the default-mode network (Zeng et al., 2023). However, these results had not been previously related to craving experiences.

Newer machine-learning approaches generate brain-behavior models from, for example, whole-brain functional connectivity data (e.g., Shen et al., 2017). Driven by data, machine-learning algorithms (e.g., support vector machines/regressions, partial least squares regressions, neural networks, or random forests) have been used to generate brain-behavior models within training datasets. In a second step, the predictive power or performance has been tested in independent/novel datasets. This step of out-of-sample prediction is important to generate more accurate and generalizable models. Connectome-based predictive modeling (CPM; Finn et al., 2015; Shen et al., 2017) is a data-driven machine-learning approach that derives brain-behavior models based on whole-brain functional-connectivity data. First, features are selected by correlating all edges of the functional-connectivity matrix with the behavioral measure (e.g., measure of craving) over all participants of a training dataset. Second, edges whose correlation-coefficient reach a specific threshold, are used as features. Third, a sum value is estimated across all selected edges and a linear model is fitted based on the brain (sum over all selected connectivity measures) – behavior (behavioral measure) relationship. CPM generally differentiates between positive networks (all positive correlation coefficients) and negative networks (all negative correlation coefficients). Fourth, the model is then applied to novel subjects (or one novel subject in a leave-one-out cross-validation), and the performance is estimated by correlating the predicted values with the actual values. Often, permutation testing is used to determine the level of significance. Due to the linear approach, CPM is not a total black-box but allows inspection of features and networks used for the prediction. While findings from such connectome-wide approaches are also complex, raising challenges for simplistic interpretations, this information can be compared to theoretical models and may also be valuable for updating existing theoretical models or deriving new hypotheses, testable in theory-driven or data-driven future work, based on mechanisms implicated in the brain-behavior relationships (Yip, Kiluk, & Scheinost, 2019).

To date and to our best knowledge, CPM has been used in four studies with the aim to predict craving (Antons, Yip, et al., 2023; Garrison et al., 2023; Yang et al., 2023; Zhou et al., 2022). In these studies, craving was predicted for alcohol (Garrison et al., 2023), cocaine (Antons, Yip, et al., 2023; Garrison et al., 2023), opioids (Yang et al., 2023), food (Garrison et al., 2023), gambling (Antons, Yip, et al., 2023) and gaming (Zhou et al., 2022). In two studies (Antons, Yip, et al., 2023; Garrison et al., 2023), the prediction was done across different types of addictions. Given that all studies used the same data-driven methodological CPM approach (despite smaller differences), consolidating the findings of these studies could provide insights into the general neural networks relevant for craving processing. Therefore, we compared, contrasted, and integrated findings across studies by considering conceptual and methodological features of the studies (Table 1). We aimed to add to existing theories by investigating the functional connectivity-craving relationship across studies and in particular across addictions.

All four studies were successful in predicting measures of craving with similar performance but different relevance of positive and negative networks: Antons, Yip, et al. (2023) (positive: $r = 0.16$, $p = 0.143$; negative: $r = 0.38$, $p = 0.009$; both: $r = 0.27$, $p = 0.038$, permutation testing), Garrison et al. (2023) (both, $r = 0.41$, $p = 0.37$, $q^2 = 0.14$, mean square error = 34.22, $p < 0.001$, permutation testing 1,000 iterations, one-tailed), Yang et al. (2023) (positive: $r = 0.027$, $p = 0.149$, negative: $r = 0.42$, $p < 0.001$, both: $r = 0.14$, $p = 0.100$) and Zhou et al. (2022) (positive: $r = 0.49$, $p < 0.001$; negative: $r = 0.02$, $p = 0.46$; both: $r = 0.31$, $p = 0.045$, permutation test).

The number of edges identified as features and the highest degree nodes differed between studies (Table 1, associations with functions described here were derived from Neurosynth if not identified by the authors, Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). Antons, Yip, et al. (2023) identified prefrontal regions implicated in executive functions and inhibitory control and regions implicated in emotion, reward processing, and face recognition. Garrison et al. (2023) identified regions implicated in memory performance and visual and sensory processing. Yang et al. (2023) identified regions relevant in processing of coordination, movement, action, sensory processing, working memory, inhibitory control and visual processing. Zhou et al. (2022) identified regions implicated in object recognition, motor planning and emotion and reward processing.

Considering canonical networks, the studies show wide overlaps of networks identified as highly relevant for the prediction of craving either because of the number of nodes selected as features or by virtual lesion approaches. A summary is presented in Fig. 1. The relevant networks identified by each study are represented in the colored circles. The default mode, motor/sensory, subcortical/basal ganglia, and visual I networks were identified in all four studies. These networks might be relevant in the prediction of craving across different methodologies and may represent

Table 1. Methodological characteristics of studies and main results

	Study by Antons, Yip, et al. (2023)	Study by Garrison et al. (2023)	Study by Yang et al. (2023)	Study by Zhou et al. (2022)
Sample	- Cocaine use disorder (N = 28, 39.29% female, DSM-IV criteria) - Gambling disorder (N = 24, 29.17% female, DSM-IV criteria)	- Alcohol use disorder (N = 38, DSM-IV criteria) - Cocaine use disorder (N = 28, DSM-IV criteria) - Obesity (N = 19, body mass index>30) - Adolescents with prenatal cocaine exposure (N = 41) - Control subjects (adult: N = 131, adolescent: N = 17) - Overall 64.72% female	- Opioid use disorder (N = 69, 62% male, DSM-5 criteria, inpatients at detoxification facilities without methadone substitution, median of abstinence: 30 days)	- Internet gaming disorder (N = 66, 50% female, met 5 DSM-5 criteria - Regular gaming (N = 61, 44.26% female, met fewer than 5 DSM-5 criteria, playing online games more that 14 h per week for min. 2 years) - All participants played the game League of Legends; further exclusion criteria (e.g., mental/neurological disorders, gambling behavior, use of illicit drugs)
fMRI task	- Cue-reactivity task with cocaine use, gambling or sad content videos - Two videos of each content type were presented - Only individuals with the target behavior (cocaine use/gambling) were used in analyses	- Personalized guided imagery task - Six scripts: two appetitive (i.e., drug, favorite food), two stress (e.g., romantic break-up), two neutral-relaxing (e.g., at beach)	- Resting-state MRI	- Cue-reactivity task (images) - Task: decision if face is visible in the picture or not and craving rating - Stimuli: 60 pictures (30 gaming-related, 30 typing related), 50% of images contained a face - Gaming-related pictures showed a person playing the online game League of Legends
Craving measure	- Before and after each video - Urges to use cocaine/ urges to gamble on a 1 "not at all" to 10 "a lot" scale - The mean of the urge measures was calculated	- Before and after each script - Desire to [use substance (e.g., drink alcohol)] at that moment/wanting of the specified food at that moment; scale 1 "not at all" to 10 "more than ever"/"extremely high" - Principal component analysis was used to summarize the six craving measures within the machine-learning process	- Heroin Craving Questionnaire, 45 items, 5 subscales, 7-point Likert scale ranging from "strongly disagree" to "strongly agree"; scale was scored at 8-month follow-up - As additional analyses change in craving was predicted	- Within task: 5-point Likert scale ranging from 1 "no craving" to 5 "extremely high craving"
CPM specificities	- Shen brain atlas that consists of 268 regions of interest - Feature selection: Spearman's rank correlation, cut-off criterion $p \leq 0.05$ - Pearson correlation for model testing - Leave-one-out cross validation - Model contribution separated into positive and negative networks	- Shen brain atlas that consists of 268 regions of interest - Feature selection: correlation, cut-off criterion $p \leq 0.05$ - Ridge regression (controlled for head motion, age, group, gender, anxiety, heart rate, smoking status) - 10-fold cross-validation for 100 random iterations - Model contribution averaged over positive and negative networks	- Shen brain atlas that consists of 268 regions of interest - Pearson correlation for model testing - Leave-one-out cross validation - Feature selection: correlation, cut-off criterion $p \leq 0.05$	- Shen brain atlas that consists of 268 regions of interest - Feature selection: correlation, cut-off criterion $p \leq 0.001$ - Pearson correlation for model testing - Leave-one-out cross validation - Model contribution separated into positive and negative networks

(continued)

Table 1. Continued

	Study by Antons, Yip, et al. (2023)	Study by Garrison et al. (2023)	Study by Yang et al. (2023)	Study by Zhou et al. (2022)
External validation	- No external validation	- Participants: Healthy participants (N = 32) fasted 10 h before the fMRI, - Task: Cue-induced food craving task (images of highly palatable foods or attractive flowers as control condition) - Craving measure: Craving was measured every 2 h during fasting (mean of 5 craving measures)	- Participants: Individuals with methamphetamine use disorder (N = 39, DSM-5 criteria) - Resting-state MRI - Craving measure: methamphetamine craving questionnaire (based on Heroin Craving Questionnaire), measured at baseline and after 8 months	- Participants: Individuals with internet gaming disorder (N = 31, also participated in the first CR task used for the CPM model); - Task: Cue-reactivity task (same as has been used for the CPM model) now after game deprivation - Craving measure: Within task (5-point Likert scale ranging from 1 "no craving" to 5 "extremely high craving")
Number of features identified	- 3,069 edges	- 1,159 edges	- 209 edges	- 66 edges
Highest degree nodes	- Dorsolateral prefrontal cortex - Dorsal posterior cingulate cortex - Inferior frontal gyrus - Orbitofrontal gyrus - Anterior prefrontal cortex - Frontal eye field - Fusiform gyrus *(Selection criterion: Degree ≥ 15)*	- Posterior cingulate cortex - Hippocampus - Visual cortex - Primary sensory areas *(Selection criterion: Top 5 % of nodes contributing to craving prediction)*	- Left limbic lobe (BA6) - Left/righ cerebellum - Right supramarginal gyrus (BA40) - Left/right motorstrip (BA6) - Left/right primary visual cortex (BA17) - Frontal eye field (BA8) *(Selection criterion: Top 10 nodes contributing to craving prediction)*	- Supplementary motor area - Inferior temporal gyrus - Orbitofrontal gyrus *(Selection criterion: Degree ≥ 6)*

the core neural networks of craving processing. Using the information from the positive and negative networks in the study by Antons, Yip, et al. (2023), there might be one network consisting of the motor/sensory, subcortical/basal ganglia, and medial frontal networks with high synchronous activity. This network, might reflect more automatic and reactive mechanisms of craving. The medial frontal network has not been identified in the study by Yang et al. (2023). As this study did not use a direct confrontation with addiction related cues but a resting-state approach, the medial frontal network as regulatory instance might have been less relevant. A second, higher-order network consisting of the fronto-parietal network integrating with salience/limbic and visual I networks may potentially reflect cognitive mechanisms of craving. The fronto-parietal-hub network (cognitive mechanism) was less consistently represented in the features of the four studies. The visual I network, that has been shown to be relevant in all four studies might represent the imaginal prefiguration as important feature of desire thinking (Brandtner, Antons, Cornil, & Brand, 2021).

As CPM is a data-driven approach, differences in results may be explained by the different tasks, stimuli, samples, craving assessments, types of addictive behaviors, and other factors. For example, the stimuli used in the studies rely on different sensory modalities (audio-visual vs. aural vs. visual only). While individualized imagery scripts as used in Garrison et al. (2023) might require consolidating memory resources (hippocampus as a high degree node), the videos shown in the study by Antons, Yip, et al. (2023) may require the processing and recognition of faces (fusiform gyrus as a high-degree node) and the video-game scenes shown in the paradigm by Zhou et al. (2022) may require identifying objects related to the game League of Legends (inferior temporal gyrus as a high-degree node). In the study by Yang et al. (2023) a resting-state paradigm was used without any cues. However, regions involved in visual processing, such as the primary visual cortex and frontal eye field, were found to be among the ten nodes with the highest degree. These may represent top-down visual processes related to imaginal prefiguration (Brandtner et al., 2021). Differences in models may also reflect samples. For example, previous studies have indicated gender effects in neural correlates of cue-reactivity and craving (Dong et al., 2018; Hallam, Boswell, DeVito, & Kober, 2016), and the CPM studies reviewed here differ in gender distributions. In addition, CPM studies focusing on other aspects of addiction, such as risky alcohol-use in youth, have demonstrated significant sex differences in model performance and in the anatomy of identified networks predictive of female vs. male alcohol use (Yip et al., 2023). The studies by Garrison et al. (2023) and Zhou et al.

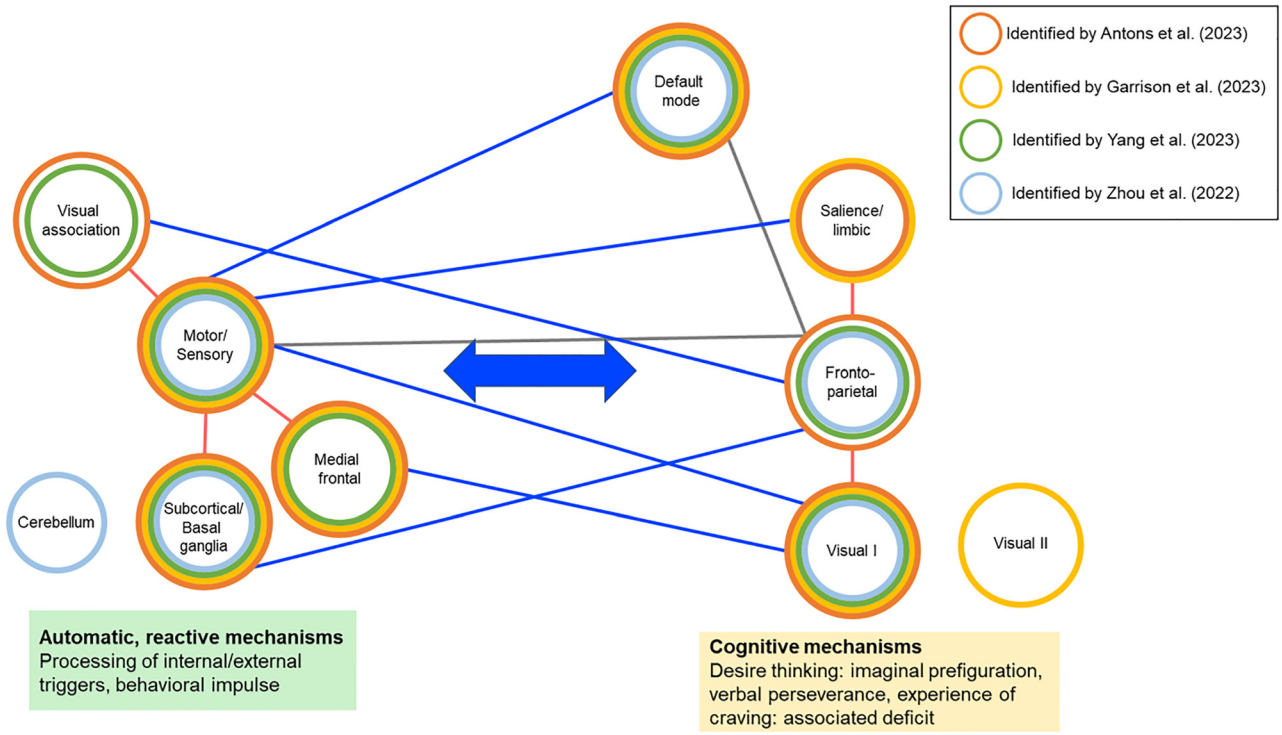

Fig. 1. Integration of the results from Antons, Yip, et al. (2023), Garrison et al. (2023), Yang et al. (2023), and Zhou et al. (2022) regarding networks predicting craving. The red, blue and grey lines were derived from the positive and negative networks observed in Antons, Yip, et al. (2023). Red lines – foremost positive connectivity, blue lines – foremost negative connectivity, grey line – both positive and negative connectivity

(2022) included control participants without clinically defined addictive disorders. By including individuals without addictions in a data-driven method, it is possible that the subjective craving measured may in part reflect affective and motivational components involved in non-problematic urges/desires. Cognitive components as identified in Antons, Yip, et al. (2023) might become particularly relevant to individuals when "getting caught up" in severe forms of craving in addictions and might not be relevant when predicting non-pathological desires/urges. On the other hand, the individualized (versus generalized) cues used in Garrison et al. (2023) may more robustly elicit craving responses which especially involve the salience/limbic system and visual components. In addition, learning mechanisms might differ between different types of addictions. Natural rewards such as food might affect associative learning differently as compared to substances forming the foundation of current substance use disorders or non-substance-related addictive behaviors like gambling or gaming (Hill-Bowen et al., 2021; van Timmeren, van Holst, & Goudriaan, 2023).

While in three of the four studies craving was assessed during cue-reactivity, Yang et al. (2023) predicted craving at 8 month follow up after a detoxification treatment. Both the timing of the craving assessment and the context of treatment might have affected craving responses and its neural correlates. The networks identified by Yang et al. (2023) are especially characterized by a high proportion of subcortical and cerebellar structures as features and their high connectivity to cortical structures (e.g., motor-network, fronto-parietal network). These results could point to the important involvement of these deep brain structures in addiction and long lasting craving responses (Miquel et al., 2016) or more stable features of craving similar to craving as a clinical characteristic (Yu et al., 2022). Additional conceptual considerations are important. The extent to which craving as a feature of substance use disorders is underpinned by the same neural mechanisms as craving in behavioral addictions and food craving in obesity or healthy individuals warrants consideration. Although overlaps could be identified across behaviors, there were also substantial differences.

Data suggest that craving might have different components involving predominantly cognitive/obsessive, automatic, or physiological elements, respectively (Antons, Liebherr, Brand, & Brandtner, 2023; Flaudias, Heeren, Brousse, & Maurage, 2019). While craving across addictive disorders and potentially related conditions (e.g., substance use disorders, behavioral addictions and obesity/binge-eating disorder) seem to have common components related to automatic, reactive processes such as action impulses (involving for example the motor/sensory network and subcortical/basal-ganglia network), they might differ in cognitive/obsessive or physiological components (involving for example a network centered around the fronto-parietal network), as can be seen by the comparison of canonical networks identified in the studies (Fig. 1). Future studies and

theories should consider automatic, reactive components of craving as central mechanisms that might be represented by interactions between the subcortical/basal-ganglia network, the motor/sensory network and the visual I network in the processing of craving. These results add to theories that center around the relevance of the ventral and dorsal striatum in addictive behaviors (Brand, 2022; Brand et al., 2019; Everitt & Robbins, 2013). The interplay between the subcortical/basal-ganglia network and further networks (motor/sensory and visual I networks) might be highly relevant as they combine, for example, the reward mechanisms with motor execution that could explain lapses during abstinence. In previous work where CPM was used to predict cocaine abstinence, a high integration between the motor/sensory network, the subcortical/basal-ganglia network and the salience network has been proposed to relate to the coordination of salience encoding and reward responding (Yip, Scheinost, Potenza, & Carroll, 2019). Based on the current and prior results, a core neural foundation of craving might reflect reward-driven motor impulses. It should be noted that the comparison of the studies presented here were of qualitative nature. However, the comparison and consolidation of findings promotes a deeper understanding of the construct of craving and which factors have been identified when using data-driven methods.

The consolidation of studies using CPM to predict craving across different behaviors indicate that processing within subcortical/basal-ganglia, motor/sensory and visual I networks may represent the neural core of craving experiences. When using data-driven methods such as CPM, it is important to consider possible effects of groups, tasks and other factors when investigating clinical constructs like craving. However, similar findings across the studies suggest common elements that might most strongly reflect networks implicated in craving, providing more robust and rigorous insight into brain networks underlying craving.

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