HHS Public Access

Author manuscript

Curr Addict Rep. Author manuscript; available in PMC 2024 December 01.

Published in final edited form as:

Curr Addict Rep. 2023 December ; 10(4): 770–792. doi:10.1007/s40429-023-00529-9.

A systematic review of sex/gender differences in the multi-dimensional neurobiological mechanisms in addiction and their relevance to impulsivity

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Abstract

Purpose of Review—Addiction may be characterized along three functional domains: Approach Behavior, Executive Function, and Negative Emotionality. Constructs underlying impulsivity thought to be relevant in addiction map on to these three functional domains. The purpose of the present review was to evaluate the extant research regarding sex/gender differences in the multi-dimensional domains of addiction using human neuroimaging and discuss their relevance to impulsivity.

Recent Findings—Few papers over the past two decades have used human neuroimaging to test sex/gender differences in addiction. There is therefore a significant gap in the literature regarding sex/gender differences in the neurobiological mechanisms driving the multi-dimensionality of addiction and their implications to impulsivity.

Summary: Of the 34 reviewed papers, the orbitofrontal cortex/ventromedial prefrontal cortex (OFC/vmPFC) was the most frequently reported brain region to evidence a sex/gender difference during fMRI tasks probing Approach Behavior and Negative Emotionality. This finding suggests

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Author contributions

Conceptualization: Andrea M Maxwell, Anna Zilverstand; Data curation: Andrea M Maxwell, Leyla Brucar; Methodology: Andrea M Maxwell, Leyla R Brucar, Anna Zilverstand; Visualization: Andrea M Maxwell; Writing - original draft: Andrea M Maxwell; Writing – review & editing: Leyla R Brucar, Anna Zilverstand; Funding acquisition: Andrea M Maxwell, Anna Zilverstand; Supervision: Anna Zilverstand.

Conflict of interest: The authors have no relevant financial or non-financial interests to disclose.

Ethics Declarations

Human and Animal Rights and Informed Consent: N/A

potential sex/gender-specific patterns of subjective valuation in substance misuse, driven by OFC/vmPFC dysregulation.

Keywords

Addiction; substance use disorder; functional neuroimaging; fMRI; sex differences; gender differences

Introduction

Substance Use Disorders (SUDs) remain one of the leading causes of preventable death across the United States [1]. According to the most recent National Survey on Drug Use and Health, over 43 million people aged 12 and over met DSM-5 criteria for a SUD in 2021, of whom only 6% of whom received treatment [2]. One challenge in both the study and treatment of SUDs is its complex dimensionality; a breadth of neurobiological, behavioral, and social factors likely contribute to both the etiology and maintenance of addiction [3–5]. Impulsivity has emerged as a key neurobehavioral component of SUDs [6]. Indeed, the now widely-accepted medical model of SUD describes addiction as a chronic health condition, characterized by 'uncontrollable, compulsive drug craving, seeking, and use, even in the face of negative health and social consequences' [7,8]. This role of impulse control in addiction is bolstered by preclinical literature suggesting that impulsivity is a key process in the development of compulsive drug-seeking behavior in rodent models [9–11]. Impulsivity itself has also been defined as a multi-dimensional construct, with different facets such as impulsive decision-making and impulsive behavior elicited by an emotional or stressful context [12,13]. Importantly, growing evidence supports sex/gender-specific patterns in different addiction-relevant mechanisms, such as stress reactivity, craving, and risky decision-making [14–17]. For example, one meta-analysis of 741 effect sizes from 277 studies found that men demonstrated greater task-related risk-taking and self-reported sensation-seeking relative to women [18]. Substance-dependent women are also more likely to report greater stress response and less stress tolerance, and are more likely to relapse to a stressful trigger relative to substance-dependent men [14,19–22]. Despite these behavioral sex/gender differences, current reviews regarding sex/gender differences in the neurobiology underlying SUDs in humans are limited, inconclusive, and, to our knowledge, restricted to a single drug of misuse [23,24]. Therefore, a systematic review of the neurobiology underlying sex/gender differences across multiple substances of misuse, and the implications for these differences in neurobehavioral processes like impulsivity, is warranted. Moreover, although historically men have endorsed SUDs more frequently than women, this gender gap is closing, driven primarily by an increase in substance use in women [25–27]. This shift further emphasizes the urgent need for such a review.

Here, we reviewed studies that assessed function across three domains that have been shown to underlie human behavior: 'Approach-related Behavior" (also referred to as 'Incentive Salience' or 'Reward Processing' in addiction neuroscience), 'Executive Function', and 'Negative Emotionality' [28]. Indeed, the National Institute of Health's Research Domain Criteria (RDOC) includes these three domains among its six key neurobehavioral domains [29]. We and others have empirically demonstrated the relevance of all three functional

domains to addiction [30–32]. Kwako and colleagues provided evidence supporting the importance of these domains in Alcohol Use Disorder (AUD) [31], and we extended these findings beyond AUD to all SUDs [30]. Impulsivity, defined as 'predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or to others', has also been shown to be a multi-dimensional construct [6,33]. Substantial work has been done to understand the constructs underlying impulsivity, leading to (among other measures), the development of the Urgency, Premeditation (lack thereof), Perseverance (lack of), and Sensation Seeking (UPPS) Impulsive Behavior Scale, and later the UPPS-Positive Urgency (UPPS-P) scale [34,35]. The UPPS-P conceptualizes impulsivity as five constructs: (1) lack of premeditation, (2) lack of perseverance, (3) sensation-seeking,(4) negative urgency, and (5) positive urgency, and its construct validity has been confirmed in substance misuse [36,37]. Importantly, these constructs parallel the three functional domains we have previously demonstrated in SUDs. Positive urgency (i.e., the tendency to act rashly under positive affect) and sensation-seeking (i.e., openness to and pursuing exciting activities) map onto the 'Approach-related Behavior' functional domain of addiction [13,38]. In contrast, the 'Executive Function' domain captures the (lack of) premeditation (i.e., the tendency to think through potential consequences of a behavior) and (lack of) perseverance (the ability to focus on tedious activities) factors of impulsivity [13,38]. Finally, negative urgency (i.e., the tendency to act rashly under negative affect) maps onto the 'Negative Emotionality' domain [13,36,38].

Previous work has further evidenced that task-based measures that capture states converge onto self-reported trait-based processes [39–41]) for all three functional domains. For example, trait-level components of neuroticism are highly predictive of symptom changes in depression and anxiety [39]. In another report, 99% of the variance attributed to a common latent factor underlying task-based executive function was explained by trait-level genetic influence [40]. Correspondingly, ecological momentary assessments of impulsive states mapped onto the heterogeneity observed for trait-level impulsivity [41]. Moreover, in a report of heavy drinkers, alcohol-related cue reactivity was positively associated with increased trait-level sensation-seeking [42]. In an independent sample of heavy alcohol drinkers, self-reported negative urgency moderated the effect of a stress induction on the reinforcing value of alcohol, which was related to increased alcohol misuse [43]. These associations between state-level task-based measures (cue reactivity and stress induction) and trait-level dimensions of impulsivity (e.g., sensation-seeking and negative urgency) evidence the convergence of state- and trait-level impulsivity on substance misuse.

Neuroimaging approaches (e.g., functional magnetic resonance imaging [fMRI]), have primarily used task-based measures to investigate function on the three domains in SUD populations. A recent systematic review of task-related fMRI in addiction found that dysregulation in brain regions underlying reward processing (e.g., nucleus accumbens [NAcc], orbitofrontal cortex [OFC], among others), during reward and socio-emotional processing tasks is related to craving, addiction severity, elevated use, and relapse across various substances of misuse [44]. Correspondingly, another review emphasized the importance of the prefrontal cortex (PFC), OFC, and amygdala as common brain regions across SUDs implicated in negative urgency [45]. Taken together, these reviews highlight

the potential role of brain regions involved in the representation of subjective value (e.g., OFC, among other regions) in both Approach Behavior and Negative Emotionality in SUDs. Reviews of fMRI studies using Executive Function tasks have most consistently found hypoactivation in the anterior cingulate cortex (ACC), inferior frontal gyrus, and dorsolateral prefrontal cortex (dlPFC) in substance-dependent samples, together suggesting that downregulation of regions involved in the executive network may be implicated in inhibitory processing across SUD populations [44,46,47].

In sum, fMRI approaches probing the processes underlying Approach Behavior, Executive Function, and Negative Emotionality in SUDs have been key in understanding the unique neurobiological mechanisms of this condition. Importantly, however, literature regarding the neurobiological mechanisms underlying sex/gender differences in these domains is scarce. In fact, across 105 task-related fMRI studies in SUD populations, only 7% conducted gender comparisons [44]. Thus, understanding sex/gender differences in the neurobiological mechanisms of these domains is essential for understanding the multi-dimensionality driving sex/gender-related patterns of behavior in addiction and their relevance for impulsivity.

In this review, we examine the extant literature in human fMRI research regarding sex/gender differences across the multi-dimensional functional domains of Approach Behavior, Executive Function, and Negative Emotionality underlying SUDs in adults and discuss their implications for impulsivity. The term ‘sex/gender’ here is used to represent the complex relationship between biological sex and the social construct ‘gender’ in brain and behavior [23,48–50]. We operationalize sex/gender as binary to be congruent with the reviewed literature. We conclude our review with providing recommendations, informed by our findings, for future work to fill the gaps in the literature.

Methodology

We performed a systematic review of studies published between 2000 and February 8, 2023. The literature search (conducted on PubMED, Embase, and PsycINFO) combined variations of keywords related to functional neuroimaging, substance dependence or Use Disorders, the 10 drug classes included in the DSM-5, and sex and/or gender differences (for exact search syntax see the Supplemental Material). We included all empirical studies that conducted sex and/or gender comparisons in adults with heavy/problematic use, abuse, dependence (DSM-IV), or Use Disorders (DSM-5) using task- or resting-state-based functional neuroimaging. The original search yielded 593 records. AMM examined each title and abstract. After removing those with exclusionary criteria, AMM and LRB reviewed the full text of all papers. After full review, 34 studies met our inclusion and exclusion criteria (Figure 1). AMM extracted data from the remaining studies, including data on both empirical findings and study design (e.g., sample size, task duration, analytic approach). Full inclusion/exclusion criteria and data extraction methods are available in the Supplemental Material. Studies were categorized into either Approach Behavior, Executive Function, or Negative Emotionality domains based on the fMRI paradigm used (Figure 2). To synthesize across studies, brain regions from each paper were grouped under a naming convention based on functional neuroanatomy, using coordinates when reported (see Supplemental Table 1). Primary findings across all reviewed studies were tallied by the grouped naming

conventions, accounting for whole brain or region of interest (ROI) approach. Study quality was evaluated considering sample size, scan length duration, and statistical analysis. The rationale and full evaluation criteria are available in the Supplemental Materials.

Results

Study Design and Methods.

A summary of the design and methods implemented in all reviewed studies is listed in Table 1; see Supplemental Material for the full reference list of all reviewed papers. Of the 34 studies reviewed, the average sample size of those with substance misuse was N = 58 (± 58). Sixteen studies also included a healthy control sample with an average sample size of N = 42 (± 39). The average number of men and women with substance misuse per sample was 33 (± 39) and 25 (± 20), respectively. The most frequently reported sample size (i.e., mode) for both men and women with substance misuse was 10 (Figure 2). The largest number of studies were conducted in people with nicotine dependence, and the most frequently used task paradigm was a drug-related cue reactivity task (Figure 2). Of the studies that reported the task or resting scan length (N=32), the average length was 19.72 ± 14.61 minutes. The majority of papers were published after 2015, the year the NIH mandated sex as a biological variable of interest in preclinical research (Supplemental Material Figure 1) [51].

Approach Behavior Functional Domain: Nineteen reviewed papers used a task-based design to measure Approach Behavior (Table 1). Overall, the OFC/ventromedial prefrontal cortex (vmPFC) was the most frequently reported brain region to indicate any sex/gender difference, with a significant finding in eight of the 18 studies (44%) that examined this area (Supplemental Figure 2, Supplemental Table 4) [52–58]. Although the OFC and vmPFC are distinct neural regions, they are functionally connected and, because the OFC is often defined as encompassing the vmPFC, both regions have been combined here for interpretation across reviewed studies [59,60]. Five of the seven studies that found a sex/gender difference in the OFC/vmPFC conducted a direct comparison between men and women with substance misuse, and the most consistent finding (80%) was increased reactivity in men relative to women in response to drug-related or positively arousing stimuli (Table 2) [53,54,57]. Generally, studies of higher quality, specifically studies with the largest sample sizes, longest scan duration, and/or most rigorous statistical analyses, most commonly reported a sex/gender difference in the OFC/vmPFC (see Supplemental Table 2 for details on the quality assessment), further bolstering this region as a potential key location for sex/gender differences. For example, Potenza and colleagues used a drug-related script imagery paradigm to assess whole-brain reactivity in 66 individuals (30 abstinent cocaine-dependent; of which 14 were women) [55]. They found a three-way interaction of sex, diagnostic group (cocaine-dependent or healthy control), and cue conditions (drug and stress scripts conditions) in the putamen, caudate, NAcc, amygdala, hippocampus, dlPFC, insula, dorsal ACC (dACC), posterior cingulate cortex (PCC), OFC, Broca's Area, and the fusiform, supplemental motor area(SMA)/motor, and temporal cortices [55]. To further explore this interaction effect, they analyzed men and women separately. They found that men with cocaine dependence demonstrated increased reactivity in the bilateral OFC and vmPFC in response to drug-related imagery compared to control men, while women did

not show this pattern [55]. Correspondingly, Study 1 of Dumais and colleagues analyzed 40 smokers (N = 23 females) using perfusion fMRI and found that men demonstrated increased reactivity to smoking (relative to non-smoking) cues compared to women in the NAcc and vmPFC [53]. Finally, Claus and colleague's 2022 analysis of 112 individuals reporting hazardous/harmful drinking (N = 49 women) found that women evidenced greater reactivity in the vmPFC, bilateral somatosensory cortex/precuneus, and left dlPFC relative to men in response to alcohol-related cues [52]. Together, these findings highlight the OFC/vmPFC as a potential key region for sex/gender differences across different substances of misuse.

Executive Control Functional Domain—Three reviewed papers used a task-based design to measure Executive Function, all assessing response inhibition by implementing a Stop Signal Task (Table 1) [61–63]. Overall, the thalamus was the most frequently reported brain region to indicate any sex/gender differences, with two of the three studies reporting a significant finding in this region (Supplemental Figure 3, Supplemental Table 5) [61,62]. Only one study conducted a direct comparison between men and women with substance misuse [63]. This study found that when measuring error processing, men exhibited increased reactivity in the precuneus and primary motor, somatosensory, parietal, and lateral occipital cortices relative to women [63]. Two studies reported sex/gender differences in brain-behavior associations involving the thalamus, such that there were sex/gender-specific relationships between thalamic connectivity and substance use behavior measures (Table 2) [61,62].

Negative Emotionality Functional Domain: Nine papers used a task paradigm to investigate Negative Emotionality (Table 1). Overall, the most frequently reported region with observed sex/gender differences was the OFC/vmPFC, with four of the nine studies (44%) reporting a significant finding (Supplemental Figure 4, Supplemental Table 6) [52,55,56,58]. Only one of the studies that found a sex/gender effect in the OFC/vmPFC conducted a direct comparison between men and women with substance misuse (Table 2) [52]. Similar to those that examined Approach Behavior, the higher quality studies reported sex/gender differences in the OFC/vmPFC (see Supplemental Table 2 for details). Potenza and colleagues found a three-way interaction between diagnosis (cocaine dependence or healthy control), sex/gender, and condition (stress- or drug-related imagery) that evidenced a significant interaction effect in the OFC, among other regions [55]. After examining men and women with cocaine dependence separately under the stress condition, they found that women with cocaine dependence demonstrated increased OFC reactivity to stressful imagery (relative to neutral imagery) compared to women without cocaine dependence (Table 2) [55]. This pattern was not observed in men with cocaine dependence. Although Claus and colleagues (2022) did not observe sex/gender differences in reactivity to negative cues in a whole-brain analysis, they did find that women with alcohol misuse exhibited increased connectivity between the NAcc, the ventral ACC and medial OFC relative to men with alcohol misuse [52]. Finally, Smith and colleagues found that in women with Alcohol and/or Cocaine and/or Cannabis Use Disorder, but not men, there was an inverse association between reactivity in the vmPFC and future days of substance use [64]. Together, similar to Approach Behavior, the findings from these more rigorous studies bolster the evidence that

the OFC/vmPFC may be a key region of neurobiological sex/gender difference underlying Negative Emotionality in addiction.

Resting-state—Ten reviewed studies used a resting-state paradigm (Table 1). The most frequently reported region to demonstrate sex/gender differences was the parietal cortex, with three of eight (38%) studies examining this region reporting a significant finding (Supplemental Figure 5; Supplemental Table 7) [65–67]. All three of these studies performed a direct comparison between nicotine-dependent men and women and found that women with nicotine dependence demonstrated increased connectivity in regions within the parietal cortices relative to men. Specifically, Li and colleagues found that women demonstrated increased brain entropy in the superior parietal lobule, Wetherill and colleagues found that women demonstrated increased cerebral blood flow between the hippocampus/amygdala and the inferior parietal lobule, and Beltz and colleagues found that women had increased connectivity between key regions of the Default Mode Network, specifically the PCC, dACC, and bilateral lateral parietal lobules [65–67].

Discussion

In this review, we characterized the current state of the literature regarding sex/gender differences in the neurobiological mechanisms underlying substance misuse in adults, as assessed by fMRI. We examined the addiction-related functional domains of Approach Behavior, Executive Function, and Negative Emotionality that parallel the multi-dimensionality observed in impulsivity. We now discuss both our synthesized findings of neurobiological mechanisms of addiction as well as broader patterns of the reviewed literature and their implications.

We found that in studies that investigated Approach Behavior and Negative Emotionality across a variety of substances, the OFC/vmPFC was the most frequently reported region to exhibit a difference between men and women with substance misuse. The most consistent finding in our review was increased reactivity in men relative to women in response to drug-related or positively-arousing stimuli, whereas women, relative to men, demonstrated increased reactivity to negative stimuli. Similarly, previous research in the general population suggested that women, in comparison to men, demonstrate selective recruitment of the OFC and amygdala to negative, threatening cues (e.g., angry faces) [68]. Furthermore, reactivity of the OFC in response to appetitive cues in a food craving task was related to levels of hunger in men but not women [69]. Both the OFC and vmPFC play key roles in computing subjective value and reward expectations [44,70,71]. Taken together, our and other's findings suggest sex/gender differences in the OFC-mediated subjective valuation of both appetitive and negative cues.

Both preclinical and human research also support a role of the OFC as a key mediator of impulsive decision-making. Individuals with OFC lesions have demonstrated increased impulsive behavior in gambling tasks [72–75]. Rodents with excito-toxic lesions of the OFC have demonstrated increased preference to larger but delayed rewards, suggesting an inability to alter preference for a reward despite a decrease in value [75]. These findings support that the OFC may facilitate updating the incentive salience of a reward

under dynamic conditions (i.e., adaptive decision-making) [75,76]. Interestingly, dissociable effects have been observed within the OFC, where lesions of the medial OFC (often equated with the vmPFC) resulted in increased preference for a larger, delayed reward, whereas lesions to the lateral OFC resulted in decreased preference for the larger, delayed reward [77]. These findings further corroborate the role of the OFC in adaptative valuation of reward.

Moreover, the OFC is considered a key brain region that may contribute to the impairment of impulse control associated with substance misuse [78,79]. Preclinical work found that increased impulsivity during withdrawal from cocaine is driven by OFC dysfunction [80]. Cocaine-induced changes in the OFC may impair adaptive behavioral control, thus lending vulnerability to less flexible, maladaptive behavior characteristic of SUDs [81,82]. Importantly, the sex/gender differences observed in OFC function may extend to addiction, as previous work suggests that men with cocaine dependence demonstrate bilateral OFC hypoperfusion while women demonstrate more limited medial OFC hypoperfusion [83]. One study examining internet gaming disorder (a behavioral addiction) found decreased vmPFC reactivity to risky decisions in affected men, while there were no group differences in women [84]. Thus, our current review contributes to the extant literature by synthesizing the evidence that supports sex/gender-based neurobiological differences in OFC/vmPFC function, particularly concerning Approach Behavior and Negative Emotionality. These findings have considerable implications for our understanding of impulsivity in addiction.

While only three of the reviewed studies investigated Executive Function, precluding any formal conclusions, previous literature supports sex/gender differences in the neural networks underlying this domain, namely response inhibition [85]. One review of 21 studies examining sex/gender differences in executive function tasks identified differences during response inhibition in the OFC, middle frontal gyrus, superior frontal gyrus, and inferior frontal gyrus [85]. Thus, it is plausible that, given more comprehensive investigation, the neurobiological sex/gender differences we find in the OFC/vmPFC may also extend to the Executive Function domain, bolstering the differential role of OFC-mediated impulsive behavior in men and women with substance misuse.

Finally, resting-state studies did not capture this OFC/vmPFC effect that we observed in the task-based fMRI studies, suggesting that task-based paradigms may be needed to investigate neurobiological sex/gender differences in SUDs linked to behavior. During resting-state, the most consistent sex/gender differences observed were found in the parietal cortex, which forms the fronto-parietal resting-state network underlying attentionally-driven executive function, a key component of cognitive control. Fronto-parietal network activity has been shown to be modulated in addiction, but recent work suggests a lack of sex differences in resting-state networks in healthy populations [86,87]. These disparate findings suggest that dysregulation in these networks may be a key sex/gender neurobiological difference in substance misuse at rest.

Importantly, these sex/gender differences in the neurobiological mechanisms in populations with substance misuse parallel work investigating the divergent patterns of impulsivity in men and women. A growing body of literature suggests that the impulsivity dimensions

captured by Approach Behavior (i.e., sensation-seeking and positive urgency) may be more pertinent to substance misuse in men, while impulsivity dimensions captured by Negative Emotionality (i.e., negative urgency) may be more pertinent to women [14,88]. For example, recent work demonstrated that higher levels of sensation-seeking was linked to driving under the influence of alcohol in men, but not in women [89]. In contrast, substance-dependent women demonstrated increased psychological and physical reactivity to stressors relative to substance-dependent men [22]. Understanding these sex/gender differences in impulse control in populations with SUDs is important because there is evidence, albeit limited, that suggests sex/gender-specific efficacy of both pharmacological and psychosocial treatments [90–93].

Given the low number of neuroimaging studies that have investigated sex/gender differences, the overall conclusions drawn from this review need to be tentative. The current state of the literature is extremely limited, with only 34 neuroimaging papers since 2000 reporting sex/gender analyses in their study of adults with SUDs. Of the 34 studies included in this review, 19 (55%) were published following the NIH mandate including sex as a biological variable in 2015, indicating that the state of sex/gender difference research in addiction neuroimaging has been evolving but slow. This lack of data is concerning, given that the closing gender gap in addiction is driven primarily by the increase in substance use in women [25–27]. Furthermore, there is significant room for improvement in the measurement of sex/gender. First, all papers implicitly assumed sex and gender as binary. Although three papers categorized participants by ‘biological sex’, these papers did not report how they measured sex (e.g., self-reported or medical records of sex assigned at birth, chromosomal analysis, and/or reproductive anatomy) [63,94,95]. Only one paper rationalized their use of the term ‘gender [96]. Recent work in both the psychological and neuroscience literature suggests that measuring both sex and gender as non-binary, multidimensional constructs may more accurately represent both brain structure/function and uncover stronger brain-behavior associations [50,97,98]. The inclusion of both gender diverse and intersex samples in clinical addiction research is crucial, as there is increased rates of Substance Use Disorders in these communities [99]. Second, only three papers examined the role of sex hormones or menstrual cycle phase (although our search terms were not designed to target neuroimaging studies examining the role of sex hormones in addiction) [55,100,101]. Recent work demonstrates dynamic sex hormone-driven functional reorganization across the menstrual cycle, suggesting a potential role of hormone-driven processes on addiction and other psychopathologies [102]. Finally, none of the studies examined the role of gendered social context, such as social support, on brain function in addiction. Investigating the neurofunctional role of social support in SUD is rare, with only one publication to date using neuroimaging to study social support, negative emotionality, and gender differences in a substance misuse population [103]. Given that our recent work has evidenced the gender-specific role of social support in SUDs, more work in this area of research is warranted [4].

The literature on sex/gender differences in substance misuse is not only limited in general, but also lacks investigations into these effects in populations with different primary drugs of use. We found that nicotine was the most frequent drug of abuse studied, with 13 of the 34 papers focusing on smokers. In contrast, there was not a single study that examined

sex/gender differences in opioid misuse. This disparity is particularly concerning, given the drastic impact of the ongoing opioid epidemic in the United States on women. Women have experienced a 642% increase in overdose deaths from 1999–2017 relative to the 439% increase in men over the same time period, yet another indication of the closing addiction gender gap driven by women [104]. The reasons for this closing gender gap are multifactorial, with both social context and sex-specific biological milieu likely playing a role. Thus, it is essential that opioid misuse be incorporated into future work on sex/gender differences in addiction.

Finally, we evaluated the quality of the reviewed studies based on three criteria: sample size, scan length duration, and statistical analyses (see Supplemental Table 2). The samples included in the reviewed papers were small to moderately sized. Only four papers included sample of at least 40 participants per group and were relatively balanced (40–60%) between men and women (Table 1 [52,63,101,105]). On average, most papers had a smaller proportion of women relative to men, and the most frequently reported sample size for both men and women with substance misuse was small at N=10 people (Figure 2). This pattern is particularly problematic given concerns about underpowered analyses, especially in brain-wide analyses of brain-behavior associations that may have small effect sizes [106]. We found that in addition to the small number of studies, challenges with data quality also impede the overall interpretability of our findings. While the average total scan length across both task and resting-state scans was about 20 minutes, the range was substantial (4 – 54 minutes). Twelve papers reported a scan duration of over 20 minutes, although two studies could not be evaluated because they did not report the duration. Twelve papers reported a scan length of less than 10 minutes duration; recent work suggests that anything below 10 minutes of resting-state data leads to low reliability estimates and systematically biased results [107]. Correspondingly, a recent meta-analysis of task fMRI studies highlights the poor test-retest reliability of fMRI tasks and proposes that both increasing sample size and the quantity of data collected per individual may be necessary to improve reliability [108]. To maintain a small to moderate (and thus more feasible) sample size, data quantity could be substantially increased by either increasing scan acquisition time or by implementing high-density sampling within a limited number of individuals [107,109,110]. Finally, just over half of the studies (N = 18) tested sex/gender differences in behavior and/or drug use variables and accounted for these confounders in the brain analyses, as appropriate. Several papers (N = 11) either did not test for potentially confounding variables or found significant sex/gender effects and did not account for these confounds in the brain analyses. There appeared to be a general trend of more consistent findings in higher quality studies, with 52% of moderate or high-quality papers that investigated Approach Behavior or Negative Emotionality reporting a sex/gender effect in the OFC/vmPFC and none of the low-quality papers.

Based on our results, we would like to highlight several opportunities for growth in the field of studying sex/gender differences in the neurobiological mechanisms of substance misuse. First, although sex/gender differences in all functional domains are understudied, research probing the neurobiological processes underlying Executive Function are particularly lacking both in number (i.e., how many papers are published) and breadth (i.e., variety of tasks). Second, future work should not only equally represent men and women in their

samples, but also integrate measures probing both gendered social context (e.g., social support) as well as sex-related neuroendocrine variables (e.g., estrogen, testosterone levels), which are woefully understudied [111]. Third, there is a need for more work probing how to accurately operationalize both sex and gender as multidimensional rather than binary constructs, and how to include both gender diverse and intersex participants in clinical addiction neuroscience research. Fourth, there is currently no work on sex/gender differences in neuroimaging of opioid dependence, which is an enormous area of clinical need that has yet to be explored. Finally, particular emphasis on improving data quality through larger sample sizes, longer scan length, higher density sampling, and/or appropriate statistical controls may aid in the reproducibility of results.

Conclusion

In conclusion, the present review describes early evidence for sex/gender differences in key regions of addiction neurocircuitry across three neurobehavioral functional domains, with implications for understanding neurobiological mechanisms underlying the multi-dimensionality of impulsivity. We have reviewed the extant literature and demonstrated that there is (1) early evidence for sex/gender differences in the OFC/vmPFC in both Approach Behavior and Negative Emotionality in addiction, with potential for this to be extended to the Executive Function domain, and (2) this evidence supports a larger role of Approach Behavior-related impulsivity dimensions (sensation-seeking and positive urgency) in men and Negative Emotionality-related impulsivity dimensions (negative urgency) in women. We also found that there is (3) an empirical demand for more nuanced and balanced practices in the inclusion, measurement, and reporting of sex and gender, (4) an urgent need for research in sex/gender differences in the neurobiology underlying opioid dependence, and (5) an increased need for improved data quality. Overall, it is imperative to bolster this scientific body of work given the incredible clinical need, especially in women with substance misuse.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank Laura E. Padilla for her review and edits.

Funding:

This work was supported by the Dr. Warren J. Warwick and Henrietta Holm Warwick Fellowship by the University of Minnesota (to AMM) and by a grant by the National Institute on Alcohol Abuse and Alcoholism (R01AA029406 to AZ).

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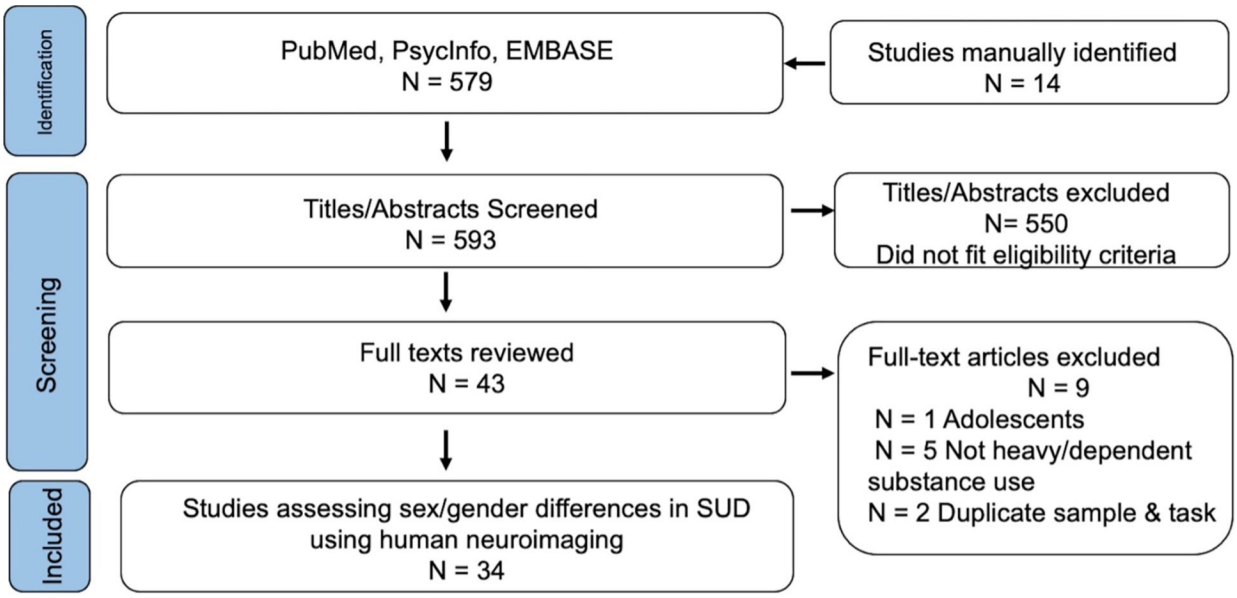

Figure 1: Study identification:
Flow diagram of paper identification, screening, and selection.

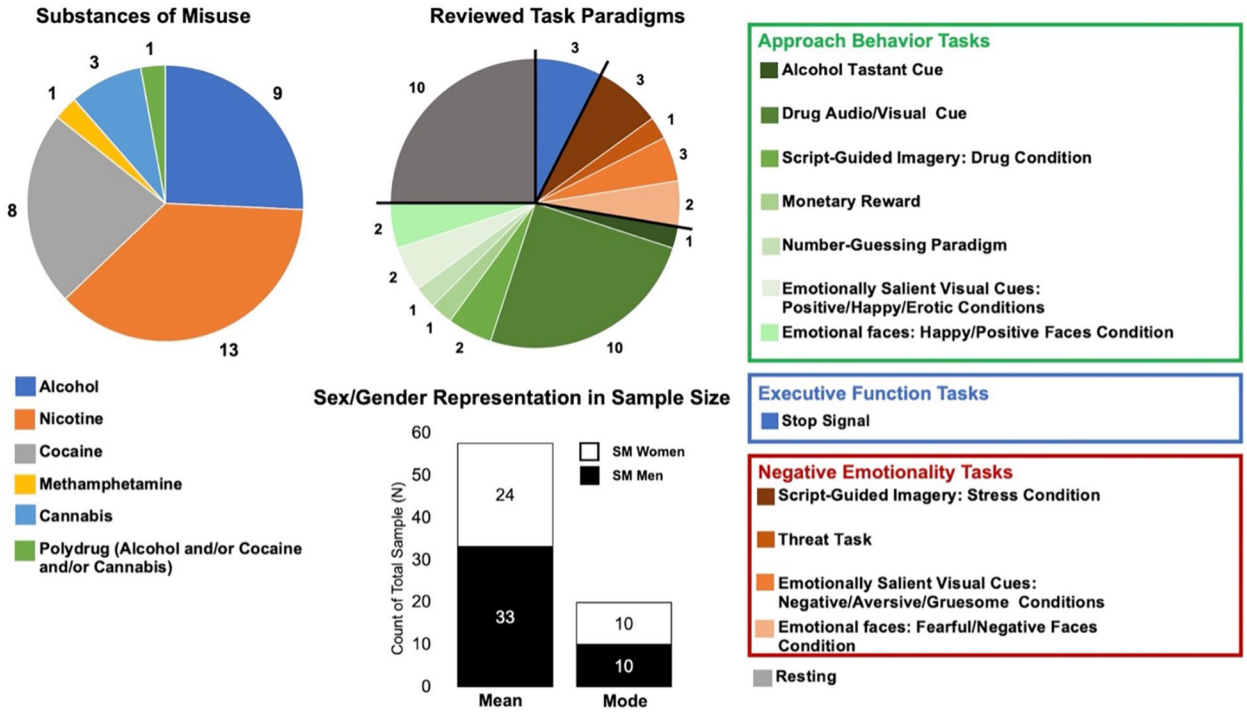

Figure 2: Investigated Populations and Task Paradigms:

The majority of studies investigated nicotine dependence, and the most frequently used task paradigm was drug-related audio/visual cues. The mean sample size of men with misuse was greater than that of women, and the most frequently reported sample size of both men and women with misuse was small at N=10. SM = substance misuse.

Table 1.

A summary of papers included in this review

Paper	Domains	Drug	Use level	Signal	Total N	SM Men N	SM Women N (% of SM)	HC Men	HC Women N (% of HC)	Task/ Resting	WB/ROI	Scan Duration (mins)	Sex or Gender Measurement
McClernon 2008	Approach	Nicotine	≥15 CPD past 2 yrs	BOLD	30	7	23 (77)	--	---	Drug Cue	WB	52	NR
Claus 2011	Approach	Alcohol	AUDIT & ADS 'Heavy'	BOLD	326	226	100 (31)	--	--	Taste Cue Task	WB & ROI	18	NR
Potenza 2012	Approach & Neg Emotion	Cocaine	DSM IV Dependence	BOLD	66	14	16 (53)	18	18 (50)	Stress & Drug Cue	WB	33[2]	NR
Nikolova 2013	Approach	Alcohol	AUDIT 'Mild–Heavy'	BOLD	138	66	72 (52)	--	--	Number-guessing	ROI	6[2]	NR
Wetherill 2013	Approach	Nicotine	FTND Dependence	CBF	51	31	20 (39)	--	--	Drug Cue	ROI	20	NR
Mendrek 2014	Approach	Nicotine	FTND Dependence	BOLD	34	15	19 (56)	--	--	Drug Cue	WB	4[2]	NR
Padula 2015	Approach & Neg Emotion	Alcohol	DSM IV Dependence	BOLD	28	6	8 (57)	5	9 (64)	Emotional Faces	WB	14	NR
Wetherill 2015	Approach	Cannabis	DSM IV Dependence	BOLD	44	27	17 (39)	--	--	Drug Cue	ROI	9	Bio Sex[3]
Canterberry 2016	Approach & Neg Emotion	Cocaine	DSM IV Dependence	BOLD	40	10	10 (50)	10	10 (50)	Emotional Stimuli	WB	9[2]	
Konova 2016	Approach	Cocaine	DSM IV Dependence	BOLD	53	14	14 (50)	14	11(44)	Monetary Reward	WB	19[2]	NR
Zanchi 2016	Approach	Nicotine	≥10 CPD past 2 yrs	BOLD	52[1]	8	10 (56)	8	9 (53)	Drug Cue	WB	20[2]	NR
Dumais 2017–1	Approach	Nicotine	FTND Dependence	CBF	40	17	23 (58)	--	--	Drug Cue	ROI	18	NR
Dumais 2017–2	Approach	Nicotine	FTND Dependence	BOLD	32	14	18 (56)	--	--	Drug Cue	ROI	12[2]	NR
Sawyer 2019	Approach & Neg Emotion	Alcohol	DSM IV Abuse or Dependence	BOLD	88	17	25 (60)	22	24 (52)	Emotional Stimuli	WB	22	NR
Molokotos 2020	Approach	Nicotine	DSM IV Dependence	BOLD	24	10	14 (58)	--	--	Drug Cue	ROI	25	NR

Paper	Domains	Drug	Use level	Signal	Total N	SM Men N	SM Women N (% of SM)	HC Men	HC Women N (% of HC)	Task/ Resting	WB/ROI	Scan Duration (mins)	Sex or Gender Measurement
Prashad 2020	Approach	Cannabis	≥5000 lifetime uses	BOLD	112	58	54 (48)	--	--	Drug Cue	ROI	28	NR[5]
Zhang 2020	Approach	Cocaine	DSM IV Dependence	BOLD	52	42	10 (19)	---	--	Drug Cue	WB, ROI,& ROI-to-WB	18	NR
Oscar-Berman 2021	Approach & Neg Emotion	Alcohol	DSM IV Abuse or Dependence	BOLD	84	21	21 (50)	21	21 (50)	Emotional Faces	WB & ROI	54	Self-Report[4]
Claus 2022	Approach & Neg Emotion	Alcohol	AUDIT 'Hazardous/ Harmful'	BOLD	112	63	49 (44)	--	--	Drug & Neg Cues	WB & ROI-to-WB	25	NR
Smith 2023	Approach & Neg Emotion	Alcohol Cocaine Cannabis	DSM IV Dependence	BOLD	72	46	26 (36)	--	---	Stress & Drug Cue	WB	30[2]	NR
Luo 2013	Exec Funct	Cocaine	DSM IV Dependence	BOLD	97	60	37 (38)	--	--	SST	WB	40	NR
Zhang 2014	Exec Funct	Cocaine	DSM IV Dependence	BOLD	108	35	19 (35)	29	25 (46)	SST	ROI-to-WB	40	NR
Swartz 2021	Exec Funct	Alcohol	AUDIT 'Hazardous'	BOLD	153	89	64 (42)	---	--	SST	WB	6	Bio Sex[3]
Li 2005	Neg Emotion	Cocaine	DSM IV Dependence	BOLD	27	17	10 (37)	--	--	Stress Cue	WB	14[2]	NR
Gorka 2019	Neg Emotion	Alcohol	DSM-5 curr/past AUD	BOLD	65	22	16 (42)	15	12 (44)	Threat Startle	ROI	7[2]	Bio Sex[3]
Chang 2002	Resting	Meth	DSM IV Dependence	CBF	40	10	10 (50)	10	10 (50)	NA	WB	NR	NR
Tanabe 2008	Resting	Nicotine	FTND Dependence	CBF	12	5	7 (58)	--	--	NA	ROI	NR	NR
Wetherill 2014	Resting	Nicotine	FTND Dependence	CBF	51	31	20 (39)	--	--	NA	ROI	5	NR
Beltz 2015	Resting	Nicotine	≥10 CPD past 1 yr	BOLD	50	27	23 (46)	--	--	NA	ROI	5	NR
Li 2016	Resting	Nicotine	FTND Dependence	BOLD	134	35	33 (49)	33	33 (50)	NA	WB	5[2]	NR
MS Maria 2017	Resting	Nicotine	FTND Dependence	BOLD	44	13	14 (52)	11	6 (35)	NA	ROI	11	NR

Paper	Domains	Drug	Use level	Signal	Total N	SM Men N	SM Women N (% of SM)	HC Men	HC Women N (% of HC)	Task/ Resting	WB/ROI	Scan Duration (mins)	Sex or Gender Measurement
Zhang 2017	Resting	Nicotine	FTND Dependence	BOLD	213	20	20 (50)	72	101 (58)	NA	ROI-to-WB	10	NR
Manza 2018	Resting	Cannabis	DSM IV Dependence	BOLD	60	22	8 (27)	20	10 (33)	NA	ROI	54	NR
Zhang 2018	Resting	Cocaine	DSM IV Dependence	BOLD	140	52	18 (26)	46	24 (34)	NA	ROI-to-WB	10	NR
Canessa 2021	Resting	Alcohol	DSM 5 AUD	BOLD	41	13	9 (41)	11	8 (42)	NA	WB	8[2]	NR

ADS = Alcohol Dependence Scale; AUD = Alcohol Use Disorder; AUDIT = Alcohol Use Disorder Identification Test; BOLD = Blood Oxygenation Level Dependent; CBF = Cerebral Blood Flow; CPD = Cigarettes per day; curr = Current DSM = Diagnostic and Statistical Manual; Exec = Executive; FTND = Fagerstrom Test for Nicotine Dependence; Funct = Function; HC = Healthy controls; Neg = Negative; NR = Not reported; Resting = Resting-state fMRI; ROI = Region of Interest; SST = Stop Signal Task; SM = Substance misuse; WB = Whole Brain; yr(s) = Year(s)

[1] Ex-smokers included in the Total N but not included in the percentage calculation as analyses from these participants are not reported here

[2] Manually estimated scan duration

[3] Reported categorization by biological sex but did not report measurement of biological sex (e.g., self-reported sex assigned at birth, chromosomal assay, reproductive anatomy)

[4] Reported that the term ‘gender’ was used because they did not measure biological sex.

Table 2:

Findings from sex/gender comparisons in reviewed papers

Study	Domains; Task	Behavioral Comparisons & Covariates	Direct Comparison SM Men v. SM Women	Interaction Effect and/or Group Differences	Brain-Behavior Associations
McClernon 2008	**Approach**; Smoking-related visual cues	Sex/gender differences **not reported** **Covariate(s):** Age, FTND, SJWQ craving & negative affect	*Smoking > Control Cue* **W > M**: R Putamen, BL cuneus, L temporal cortex, L Motor/SMA **M > W**: L Hippocampus and L OFC	---	**M**: Cue reactivity in the hippocampus was positively associated with negative affect **W**: No brain-behavior associations
Claus 2011	**Approach**; Taste Cue Task	Sex/gender differences **not reported** **Covariate(s):** ADS	*Alcohol > Control Beverage* *Whole brain analysis*: No main effect of sex/gender *ROI Analysis:* **M > W** in L Amygdala	---	Not reported
Potenza 2012	**Approach & Negative Emotionality**; Stress & Drug Imagery Script	**No sex/gender difference** in cocaine use or cue-elicited craving, anxiety, heart rate **Covariate(s):** None	----	**3-way interaction of sex, diagnostic group, and condition**: R temporal cortex, putamen, amygdala, hippocampus, insula, PCC, Fusiform cortex, L caudate, NAcc, dlPFC, SMA, BL Broca's Area, OFC Directions explored separately: *Drug Condition:* **M**: **CUD > HC** in ACC, PCC, L thalamus, BL insula, BL caudate, BL hippocampus, BL putamen, BL dlPFC, BL vmPFC, BL OFC **W**: **CUD < HC**: Cerebellum, BL ACC, BL PCC, L Primary Sensory & Motor, Parietal Cortex *Stress Condition:* **M: CUD > HC** in cerebellum, ACC, NAcc, thalamus, insula; **CUD < HC** in precuneus **W: CUD > HC** in ACC, PCC, BL vmPFC, BL dmPFC, L dlPFC, BL insula, BL OFC, BL amygdala, BL hippocampus, R NAcc	*Drug > Neutral:* **M**: Positive association between craving and reactivity in the hippocampus, insula, PCC, dlPFC, dmPFC, temporal and parietal cortices, cerebellum **W**: Positive association between craving and reactivity in the midbrain, hippocampus, vlPFC, temporal cortex, cerebellum, thalamus *Stress Condition > Neutral:* **M**: Positive association between craving and reactivity in the BL occipital cortex **W**: No brain-behavior associations
Nikolova 2013	**Approach**; Number-guessing	**M > W** problem drinking **Covariate(s):** Current Axis 1 Diagnosis, Age	*Positive > Negative Feedback* CA haplotype carriers only: **M > W** in BL NAcc reactivity	---	**M**: Increased NAcc reactivity mediated an association between CA haplotype and increased problematic drinking **W**: Decreased R NAcc reactivity mediated an association between CA

Study	Domains; Task	Behavioral Comparisons & Covariates	Direct Comparison SM Men v. SM Women	Interaction Effect and/or Group Differences	Brain-Behavior Associations
					haplotype and decreased problematic drinking
Wetherill 2013	**Approach**; Smoking-related audio/visual cues	**M > W**: CPD & Pack-years **W > M:** Cue-elicited craving **Covariate(s):** CPD	*Smoking > Neutral Cue* **M > W**: Activity in BL clusters in the hippocampus and amygdala to smoking cues	---	Craving was not associated with brain reactivity in either men or women
Mendrek 2014	**Approach**; Smoking-related visual cues	**No sex/gender differences** in basal or cue-induced craving, depressive symptoms **Covariate(s):** None	*Smoking-related > Smoking Unrelated Cues* **No** sex/gender differences	----	Not reported
Padula 2015	**Approach & Negative Emotionality**; Emotional Faces	Sex/gender differences **not reported** **Covariate(s):** Age, Handedness, Task Accuracy	Not reported	Interaction effect: *Fearful > Neutral faces:* **M AUD > M HC** while **W AUD < W HC** in the BL OFC *Happy > Neutral Faces*: **M AUD > M HC** while **W AUD < W HC** in L caudate, L OFC, L Parietal cortex and R Occipital cortex	Not reported
Wetherill 2015	**Approach**; Backward-Masked Cue Task	**No sex/gender differences** in cannabis use behaviors or craving **M > W** # weekly drinkers **Covariate(s):** Age, weekly quantity and frequency of substance use; HAM-D/A	**No** sex/gender differences	----	**M**: Baseline cannabis craving positively associated with striatum activation to cannabis cues **W:** Baseline cannabis craving positively correlated with bilateral anterior insula activation to cannabis cues; inversely correlated with the L lateral OFC activity
Canterberry 2016	**Approach & Negative Emotionality**; Emotional Stimuli	**No sex/gender differences** in demographics, cocaine use behavior, or other clinical variables; **No sex/gender** differences on arousal rating to cues **Covariate(s):** Depression symptomology, education, state anxiety, CPD	*Arousing Positive > Neutral Cues* **M > W** in the R OFC *Arousing Negative > Neutral Cues* **No** sex/gender differences	*Arousing Positive > Neutral* **M:** No significant differences **W: CUD < HC** in OFC, vACC, PCC, angular gyrus *Arousing Negative > Neutral* **M:** No significant differences **W: CUD < HC** OFC, ACC, fusiform cortex, L temporal cortex, putamen	Not reported
Konova 2016	**Approach**; Monetary Reward	**M < W** task reaction time; **No sex/gender differences** in cue-elicited cocaine craving or cocaine use behaviors; Female cocaine users more likely to report lifetime mood disorders relative to male cocaine users **Covariate(s):** Age, BDI scores, and reaction times	**W < M** in R Hippocampus, BL PCC, L temporal cortex	**SUD W < SUD M**, **HC W** in R primary Motor **SUD W > SUD M**, **HC W** in L Broca's Area	**No** sex/gender differences in brain-behavior associations

Study	Domains; Task	Behavioral Comparisons & Covariates	Direct Comparison SM Men v. SM Women	Interaction Effect and/or Group Differences	Brain-Behavior Associations
Zanchi 2016	**Approach**; Smoking-related audio-visual cues	**No sex/gender differences** in smoking behavior or cue-elicited craving **Covariate(s):** None	*Smoking > Neutral Cue* **W > M**: Activity in the dlPFC, Broca's Area, dACC, and temporal and occipital cortices	Sex/gender difference in dlPFC, Broca's Area, dACC, and precuneus was greater in smokers relative to non-smokers	Craving was not associated with brain reactivity in either **M** or **W**
Dumais 2017 Study 1	**Approach**; Smoking-related audio-visual cues	**M > W** pack-years **No sex/gender differences** in basal or cue-induced raving **Covariate(s):** Pack-years	*Smoking > Neutral* **M > W** reactivity in the NAcc and vmPFC	----	**M**: Change in pre- to post- scan craving was positively correlated with NAcc reactivity **W**: No brain-behavior associations
Dumais 2017 Study 2	**Approach**; Smoking-related visual cues	**M > W** cigarettes per day **No sex/gender differences** in basal or cue-induced craving **Covariate(s):** CPD	*Smoking > Neutral* **M > W** in bilateral vmPFC	---	M: Positive association between post-SC craving in and entire ROI mask (encompassing all listed regions) **W**: No brain-behavior associations
Sawyer 2019	**Approach & Negative Emotionality;** Emotional Stimuli	**AUD W < AUD M** average # daily alcoholic drinks & sensation-seeking **AUD W > AUD M** delayed memory scores & Wechsler Memory Scale **Covariate(s):** None	Tested but region-specific results not reported	*Happy and Erotic > Neutral:* **AUD M < HC M** in BL OFC, BL dlPFC, L parietal cortex, BL SMA, L Occipital cortex, L precuneus, L cuneus, L dACC, L cerebellum; W either did not exhibit these decreases or exhibited increases *Aversive and Gruesome > Neutral:* **AUD M < HC M** in L dmPFC, R OFC and L dlPFC, BL SMA, L parietal cortex, L temporal cortex, L cerebellum; W either did not exhibit these decreases or exhibited increases	Not reported
Molokotos 2020	**Approach;** Smoking-related visual cues	**No sex/gender differences** in smoking behavior or demographics **Covariate(s):** Discriminability on PRT task	Not reported	---	**M**: Out-of-scanner PRT response bias positively associated with L caudate reactivity **W**: No association between PRT and brain reactivity
Prashad 2020	**Approach**; Visual Drug Cue	**M > W** number of alcohol drinking days and number of drinks **W > M** subjective cannabis craving **Covariate(s):** None	**No** sex/gender differences in neural response	---	Not reported
Zhang 2020	**Approach**; Cocaine-related visual cues	**No sex/gender differences** in cocaine use measures or craving **CUD W > CUD M** on BDI score, age	*Whole brain analysis:* **No** sex/gender differences *ROI: PAG Activity:* **No** sex/gender differences	---	*PAG Activity:* **No** sex/gender differences *PAG Connectivity* M: PAG -- vmPFC connectivity

Study	Domains; Task	Behavioral Comparisons & Covariates	Direct Comparison SM Men v. SM Women	Interaction Effect and/or Group Differences	Brain-Behavior Associations
		Covariate(s): Age, Years of drinking, BDI scores	*PAG Connectivity* **No** sex/gender differences		positively associated with craving W: PAG – vmPFC connectivity negatively associated with craving *Granger Causality analysis:* M: PAG → vmPFC W: vmPFC → PAG
Oscar-Berman 2021	**Approach & Negative Emotionality;** Emotional Faces	**AUD W < AUD M** Duration of Heavy Drinking in Years **AUD W > AUD M HAM-D/A** **Covariate(s):** None	*Whole brain analysis:* **No** sex/gender differences *ROI analysis* **No** sex/gender differences	*Whole brain analysis:* *Positive > Fixation* **HC W > AUD W**, differences in L temporal cortex, but not between in **M** *Negative > Fixation* **AUD M > HC M**, differences in L FEF, but not in **W** *ROI analysis:* Emotion X Group X Sex/ Gender: In **HC M** and **AUD W**: Greater reactivity to positive faces (vs. fixation) relative to negative and neutral faces compared to AUD men and HC women in L hippocampus	Not reported
Claus 2022	**Approach & Negative Emotionality**; Alcohol & Negative Cues	**No sex/gender differences** in alcohol use behaviors **W > M** in craving, sadness, fear affect, and perceived stress; **M > W** in self-efficacy **Covariate(s):** None	*Alcohol > Neutral Cues* Whole brain analysis: **W > M** in the bilateral somatosensory cortex/precuneus, L dlPFC, and vmPFC ROI analysis: No main effect of sex/gender *Negative > Neutral Cues* Whole brain analysis: No main effect of sex/gender ROI analysis:**W > M** in L NAcc – vACC and L NAcc – medial OFC connectivity	---	Not reported
Smith 2023	**Approach & Negative Emotionality;** Stress & Drug Imagery Script	**SUD M > SUD W** years of substance use **SUD W > SUD M** history of trauma, lifetime PTSD, anxiety ratings to drug cues with same pattern at the trend-level for stress cues; **No** sex/gender main effect on craving, heart rate, anxiety **Covariate(s):** CTQ and significant sex differences in any demographic variable included as a covariate in all analyses	*Drug Cues (Drug > Neutral):* **No** sex/gender differences *Stress Cues (Stress > Neutral):* **M > W** in the BL caudate, thalamus, hypothalamus, R hippocampus, and L putamen	---	*Drug Cues:* **M**: Positive association between reactivity in the putamen and caudate and # of follow-up days of substance use **W**: Inverse association between reactivity in the L dlPFC and L insula and future number of days used *Stress Cues:* **M**: No brain-behavior associations

Study	Domains; Task	Behavioral Comparisons & Covariates	Direct Comparison SM Men v. SM Women	Interaction Effect and/or Group Differences	Brain-Behavior Associations
					W: Inverse association between reactivity in the vmPFC and future days of substance use
Luo 2013	**Executive Function;** Stop Signal Paradigm	**No sex/gender differences** in craving or task performance **W > M** # days used cocaine **M > W** # years of alcohol use **Covariate(s):** Years of cocaine and alcohol use, amount of cocaine and alcohol use in the month before admission	Not reported	---	*Stop Error > Stop Success* **M:** Decreased left insula and dACC activation predicted relapse and earlier time to relapse **W:** Decreased thalamic and dACC activation predicted relapse and earlier time to relapse
Zhang 2014	**Executive Function;** Stop Signal Paradigm	Sex/gender differences in cocaine use measures, craving, and task performance **not assessed** **Covariate(s):** Days of abstinence	*Stop Error > Stop Success* Not reported	Not reported	**M**: No brain-behavior associations **W**: Thalamus – vmPFC connectivity was positively correlated with the amount of cocaine use in the month before admission
Swartz 2021	**Executive Function**; Stop Signal Paradigm	**No significant first-order correlation** between sex/gender and AUDIT scores or age Sex/gender differences in other clinical measures (anxiety, mood) **not statistically tested** **M < W** RT on 'Go' Trials **Covariate(s):** Diagnosis of mood or anxiety disorder, self-reported use of cannabis in the previous 90 days	*Correct Stop > Correct Go* **No** sex/gender differences *Incorrect Stop > Correct Go:* **M > W** reactivity in the primary motor cortex/ somatosensory cortex, parietal cortex, precuneus, lateral occipital cortex *Correct stop > Incorrect stop* **No** sex/gender differences	---	**M:** Negative association between reactivity in the somatosensory and lateral occipital cortex and AUDIT score **W**: Positive association between reactivity and AUDIT score in the somatosensory and lateral occipital cortex
Li 2005	**Negative Emotionality;** Stress Imagery Script	**No sex/gender differences** in cue-elicited heart rate, anxiety, craving, or vividness rating of imagery **No sex/gender differences** in cocaine measures **Covariate(s):** None	**W > M**: L FEF, L vACC, R PCC, L Broca's Area, L insula	---	**M**: No brain-behavior associations **W:** R PCC reactivity inversely correlated with cocaine craving and positively correlated with change in heart rate
Gorka 2019	**Negative Emotionality;** Threat Startle Response	Sex/gender differences in demographics, alcohol use behaviors, craving, or task performance **not reported** **Covariate(s):** None	**No** main effect of sex/gender	**No** interaction effect	**No** Brain X Sex/Gender Interaction of behavioral measures
Chang 2002	Resting	Sex/gender differences in methamphetamine use behavior, demographics, or behavior **not reported** **Covariate(s):** None	Not reported	Interaction Effect: **W: MD > HC** R occipital cortex and midline structure (pineal gland) **M: MD < HC** R occipital cortex and midline structure (pineal gland)	Not reported

Study	Domains; Task	Behavioral Comparisons & Covariates	Direct Comparison SM Men v. SM Women	Interaction Effect and/or Group Differences	Brain-Behavior Associations
Tanabe 2008	Resting	**No sex/gender differences** in smoking behavior or age **Covariate(s):** None	**No** main effect of sex/gender	----	Not reported
Wetherill 2014	Resting	**M > W** CPD **Covariate(s):** None	**W > M** connectivity between the hippocampus/amygdala and bilateral AI, vACC, & L parietal cortex	---	Not reported
Beltz 2015	Resting	**No sex/gender differences** in smoking behavior **Covariate(s):** Age, CO in analyses related to nicotine dependence/tolerance	**W > M** in Default Mode Network (PCC, dACC, BL parietal cortex)	---	**M:** No brain-behavior associations **W:** Positive correlation between nicotine tolerance and connectivity within the reward network (bilateral striatum, OFC)
Li 2016	Resting	Sex/gender differences in alcohol use measures, craving, and behavior **not reported** **Covariate(s):** Age	**W > M** BEN in L primary motor, BL somatosensory, BL temporal, L parietal, and R occipital cortices, precuneus, R cerebellum	Smokers had less widespread resting BEN difference between men and women relative to HC	**M**: Positive association between BEN and years-smoking in R premotor/SMA; Negative association with R cuneus, L occipital cortex, R OFC; *Further correlations between BEN and CPD, FTND) (see Li et al*supplemental material) **W:** Positive association between BEN and years-smoking in R amygdala, BL Broca's area, R primary motor, BL temporal, parietal, occipital cortices; further correlations between BEN and CPD, FTND*) (see Li et al*supplemental material)
MS Maria 2017	Resting	**No sex/gender differences** in demographics, smoking behavior or dependence **Covariate(s)**: None	**No** sex/gender differences	Not reported	**W:** No brain-behavior associations **M:** Positive association between EVC and FTND in R insula; trend-level positive association between DIV and FTND in the L NAcc
Zhang 2017	Resting	**M > F** years of tobacco use Compared to HC, **W** but not men smokers reported greater narcotics and marijuana use **Covariate(s):** Age, Years of marijuana use, Days of marijuana use in the prior month	Not reported	**No** interaction effect**. M** and **W** analyzed separately: **M: Smokers > Nonsmokers**: None Nonsmokers > Smokers: None **W: Smokers > Nonsmokers**: SMA, somatosensory and parietal cortices, anterior insula; **Smokers < Nonsmokers:** PCC/precuneus	**M:** BNM-SMA connectivity negatively correlated with FTND **W:** No brain-behavior associations
Manza 2018	Resting	Sex/gender effects on cannabis use measures and craving **not reported** **Covariate(s):** None	**No** sex/gender differences	**No** sex/gender differences	Not reported

Study	Domains; Task	Behavioral Comparisons & Covariates	Direct Comparison SM Men v. SM Women	Interaction Effect and/or Group Differences	Brain-Behavior Associations
Zhang 2018	Resting	Sex/gender effects on methamphetamine use, craving, task performance **not reported** **Covariate(s):** Age, Smoking status	Not reported	Interaction effect: **M: CD < HC** MH-dmPFC connectivity **W: CD > HC** MH-dmPFC connectivity	**M:** No brain-behavior associations **W:** MH-dmPFC connectivity is negatively associated with craving
Canessa 2021	Resting	**No sex/gender differences** in alcohol use behavior **No sex/gender differences** in out-of-scanner task performance; **Covariate(s):** Age, smoking status	Not reported	**No** Sex X Group effects	**No** Sex X Group X Decision-latency effects on resting-state metrics

ADS = Alcohol Dependence Scale; AUD = Alcohol Use Disorder; AUDIT = Alcohol Use Disorders Identification Test; BDI = Beck Depression Inventory; BEN = Brain Entropy; BL = Bilateral; BNM = Basal Nucleus of Meynert; CA = haplotype of GAL gene; CD = Cocaine-dependent; CO = Carbon monoxide CPD = Cigarettes smoked per day; CTQ.= Childhood Trauma Questionnaire; CUD = Cocaine Use Disorder; dACC = dorsal anterior cingulate cortex; DIV = Diversity coefficient; dlPFC = dorsolateral prefrontal cortex; dmPFC; = dorsomedial prefrontal cortex; EVC = Eigenvector centrality; FTND= Fagerstrom Test for Nicotine Dependence; FEF = Frontal eye field; HAM-D/A = Hamilton Depression Rating scale; Hamilton Anxiety Rating Scale; HC = healthy control L = Left; M = Men; MD = Methamphetamine-dependent; MH = Medial hypothalamus; NAcc = Nucleus Accumbens; OFC = Orbitofrontal cortex; R = Right; Pack-years = Quantification of the amount an individual has smoked, calculated by the number of packs smoked per day multiplied by the number of years the individual has smoked; PAG = Periaqueductal gray; PCC= Posterior cingulate cortex; PTSD = Post-Traumatic Stress Disorder; PRT = Probabilistic reward task; SJWQ = Shiffman-Jarvik Withdrawal Questionnaire; ROI = Region of Interest; RT = Reaction Time; SM = Substance misuse; SMA = Supplemental motor area; SUD = Substance use disorder; vACC= Ventral anterior cingulate cortex; vlPFC = Ventrolateral prefrontal corte; vmPFC= Ventromedial prefrontal cortex; W = Women