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Functional Domains of Substance Use and their Implications to Trauma: A Systematic Review of Neuroimaging Studies

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Abstract

Substance use disorder (SUD) is a significant health problem, and trauma exposure is a known risk factor for the escalation of substance use. However, the shared neural mechanisms through which trauma is associated with substance use are still unknown. Therefore, we systematically review neuroimaging studies focusing on three domains that may contribute to the overlapping mechanisms of SUD and trauma—reward salience, negative emotionality, and inhibition. Using PRISMA guidelines, we identified 45 studies utilizing tasks measuring these domains in alcohol, tobacco, and cannabis use groups. Greater reward, lesser regulation of inhibitory processes, and mixed findings of negative emotionality processes in individuals who use substances versus controls were found. Specifically, greater orbitofrontal cortex, ventral tegmental area, striatum, amygdala, and hippocampal activation was found in response to reward-related tasks, and reduced activation was found in the inferior frontal gyrus and hippocampus in response to inhibition-related tasks. Importantly, no studies in trauma-exposed individuals met our review criteria. Future studies examining the role of trauma-related factors are needed, and more studies should explore inhibition- and negative-emotionality domains in individuals who use substances to uncover clinically significant alterations in these domains that place an individual at greater risk for developing a SUD.

Keywords

substance use, reward, inhibition, negative emotionality, trauma, functional magnetic resonance neuroimaging

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Introduction

A substance use disorder (SUD) develops upon continued substance use despite experiencing problems due to consumption.[1] SUD is considered a severe public health crisis. About 20.4 million people in the United States were diagnosed with a SUD in the past year.[2] According to the diagnostic criteria, there are a total of 11 symptoms a person may exhibit, including those associated with impairments in inhibitory control, cravings/urges to use the substance, needing more of the substance to achieve the desired effect (tolerance), and withdrawal effects that can only be improved by taking more of the substance.[1] SUDs may be associated with adverse physical and mental health outcomes on the individual level and exert large negative consequences on the societal level. For example, SUD patients experience an increased risk of suicidal outcomes[3] and social, academic, and work impairment.[4] Societally, the US suffers billions in annual productivity loss related to lost wages and productivity, crime, and healthcare expenses due to SUD.[5] Rates of SUD have dramatically increased following the onset of the COVID-19 pandemic,[6] especially in underserved communities.[7] Thus, it is vital, now more than ever, to better understand

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the mechanisms that potentially underlie the development of an SUD.

A neurobiological framework for the transition from controlled drug use to unhealthy use (ie, addiction) has been proposed that is comprised of three stages: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation.[8] In their 2016 review, the authors build on this work by outlining a heuristic framework focusing on three functional domains: reward salience, negative emotionality, and executive function, which overlap with the three-stage addiction cycle, and identify neural circuits mediating each domain.[9] The binge/intoxication (reward salience) stage highlights regions of importance, including areas of the basal ganglia, such as the nucleus accumbens, ventral tegmental area (VTA), and ventral pallidum/substantia innominata. During the withdrawal/negative affect stage (negative emotionality), the extended amygdala is important, with projections to the hypothalamus and brainstem. The preoccupation/anticipation phase is defined as deficits in executive functioning and inhibition and recruits regions such as the anterior cingulate cortex (ACC) and prefrontal cortex.[9]

Trauma exposure is a common risk factor for developing or worsening substance use and SUDs.[10-14] Indeed, trauma contributes to the onset of substance misuse,[15,16] and substance misuse can lead to exposure to more trauma.[17] However, the underlying mechanism by which trauma contributes to substance misuse, and vice versa, is still largely unknown.[18] Some individuals who experience trauma may develop posttraumatic stress disorder (PTSD). PTSD is a debilitating disorder with a lifetime prevalence rate of 8% in the general population[19] and is highly comorbid with SUDs.[20]

In the past three decades, much work has been done to elucidate the neural correlates of PTSD, and many reviews have been published on the topic.[21-30] Classical neurocircuitry models of PTSD highlight exaggerated activation of the amygdala, followed by poor regulatory control of the amygdala from prefrontal cortical regions.[31]

There have been a handful of review papers that have explored the neural overlap between PTSD and SUD.[32-34] Hien et al[34] proposed a translational framework designed to advance the creation of interventions for co-occurring PTSD and SUD through understanding the overlapping mechanisms associated with each disorder. Building upon previous work on the Research Domain Operating Criteria (RDoC)[35] and its counterpart, Alcohol and Addiction Research Domain Criteria (AARDoC),[36] the authors highlight the functional domains proposed by Koob and Volkow,[9] providing an overview of studies that assess behavioral deficits and biological alterations associated with each domain separately for PTSD, SUD, and co-occurring PTSD + SUD. One limitation of Hien and colleagues' review is the lack of an in-depth synthesis of the discussed neuroimaging studies exploring each functional domain. Given the many new developments in the neural mechanisms on this topic, a systematic review of neuroimaging findings related to the functional domains highlighted by Koob and Volkow[9] is warranted to explain the neural mechanisms underlying SUD development and explore their potential implications in trauma-exposed samples.

This review systematically synthesizes neuroimaging studies focusing on three domains that may contribute to the overlapping mechanisms of SUD and PTSD—reward salience, negative emotionality, and executive function. Within this framework, we separately review studies that either used or did not use explicit measures of trauma exposure, enabling us to draw conclusions from and identify knowledge gaps for each population. Lastly, previous research has found alcohol, cannabis, and tobacco use to be the most used substances by trauma-exposed individuals.[37] As such, we will focus on these three substances within the review. After reviewing the neuroimaging literature, we suggest future research integrating these findings with trauma.

Methods

The Supplemental Materials provide a brief overview of the neuroimaging techniques used and an in-depth description of each pathway, including regions of interest (ROIs).

Eligibility

The systematic review was conducted according to the guidelines set by the Preferred Report Items for Systematic Reviews and Meta-analysis (PRISMA), without preregistration. We conducted two literature searches. The first search focused on individuals who use substances to investigate neurobiological mechanisms of the three domains irrespective of trauma exposure. The second search focused on trauma-exposed individuals who use substances to explore potential neurobiological characteristics of the three domains related to trauma exposure. Eligibility criteria for the first literature search included: 1) original empirical reports; 2) published in English; 3) used the following neuroimaging techniques: functional magnetic resonance imaging (fMRI)—with or without blood oxygen level-dependent (BOLD)—and positron emission tomography (PET); 4) included a control group in analyses. Exclusion criteria included: 1) meta-analyses/review articles; 2) studies in languages other than English; 3) studies containing only healthy subjects; 4) studies that did not contain a control group; 5) studies that did not make group comparisons; 6) studies that utilized long-term abstinent experimental groups; 7) studies using adolescent or child samples; 8) experimental group was a treatment-seeking sample; 9) intervention or substance was administered during imaging procedures; 10) structural imaging techniques were used; 11) family history of substance use was explored, but not personal substance use in the experimental group; 12) animal studies; and 13) tasks that do not measure any of the three domains was not used. Eligibility and exclusion criteria for the second literature search were like the

first, including 14) a group of trauma-exposed individuals who use substances as an eligibility criterion.

Search Strategy

For the first literature search, we used PubMed, Web of Science, and Google Scholar and a combination of the following terms and Booleans in the title/abstract of articles: (inhibition OR impulsivity OR impulsiveness); (reward); (anxiety OR anhedonia OR fear OR threat) AND (substance use disorder OR substance abuse OR substance use OR substance misuse OR alcohol abuse OR alcohol use disorder OR alcohol use OR addiction) AND (neuroimaging OR functional magnetic resonance imaging OR fMRI OR functional MRI OR positron emission tomography OR PET). For the second literature search, we used the same databases, including the combination of the above terms, with the addition of AND (PTSD OR trauma OR posttraumatic stress disorder).

Study Selection

Four independent reviewers (CAH, JZ, JB, and SVR) screened study titles and abstracts for inclusion with a consensus on selection criteria. Data extraction forms were extracted by three reviewers (JZ, JB, and SS) and checked by two reviewers (CAH and SVR). All reviewers resolved any remaining inconsistencies.

The following information was gathered from the articles: sample size for each experimental and control group, the biological sex breakdown of each group, the mean age for each group, study design and methodology, and direction of activation for the brain regions of interest (ie, brain areas activated related to the three proposed domains).

Results

Study Characteristics

Refer to Figure 1 for the PRISMA diagram with a breakdown of the literature reviewed across all domains for the first literature search. In all, 45 articles met the inclusion criteria outlined above ($n = 1195$ substance use, $n = 1291$ controls), published from 2001 to 2022. Of the 45 studies, 30 were specific to the reward literature, nine to the inhibition literature, and six to the anxiety sensitivity literature. One study was included for both reward and inhibition domains. For the reward domain, of the 31 studies, 14 focused on alcohol ($n = 412$ individuals that use alcohol, $n = 398$ controls), 12 on tobacco ($n = 224$ individuals that use tobacco, $n = 231$ controls), and five on cannabis ($n = 142$ individuals that use cannabis, $n = 192$ controls). For the inhibition domain of the nine studies, five focused on alcohol ($n = 151$ individuals that use alcohol, $n = 168$ controls), and four on tobacco ($n = 92$ individuals that use tobacco, $n = 86$ controls) as the substance of interest. Lastly, for the negative emotionality domain, of the six studies, four focused on alcohol ($n = 131$ individuals that use alcohol, $n = 177$ controls), one on tobacco ($n = 28$

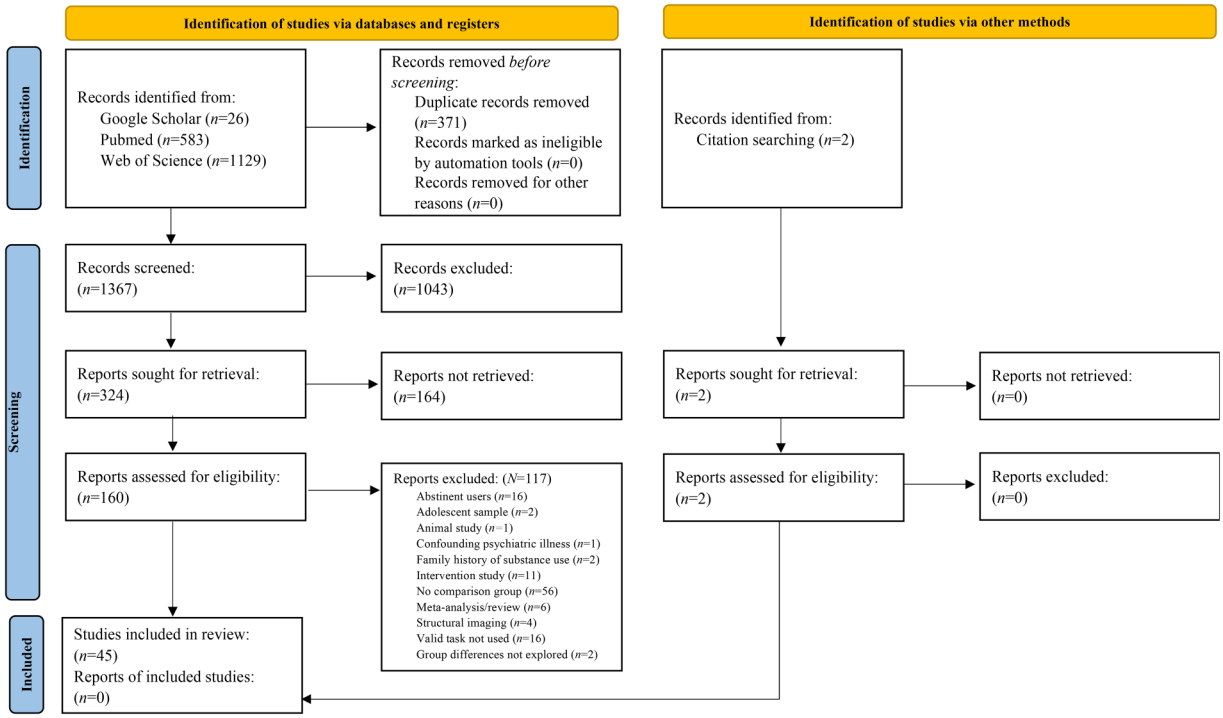

Figure 1. Flow diagram of literature search results from identification to inclusion for studies where trauma exposure is not measured.

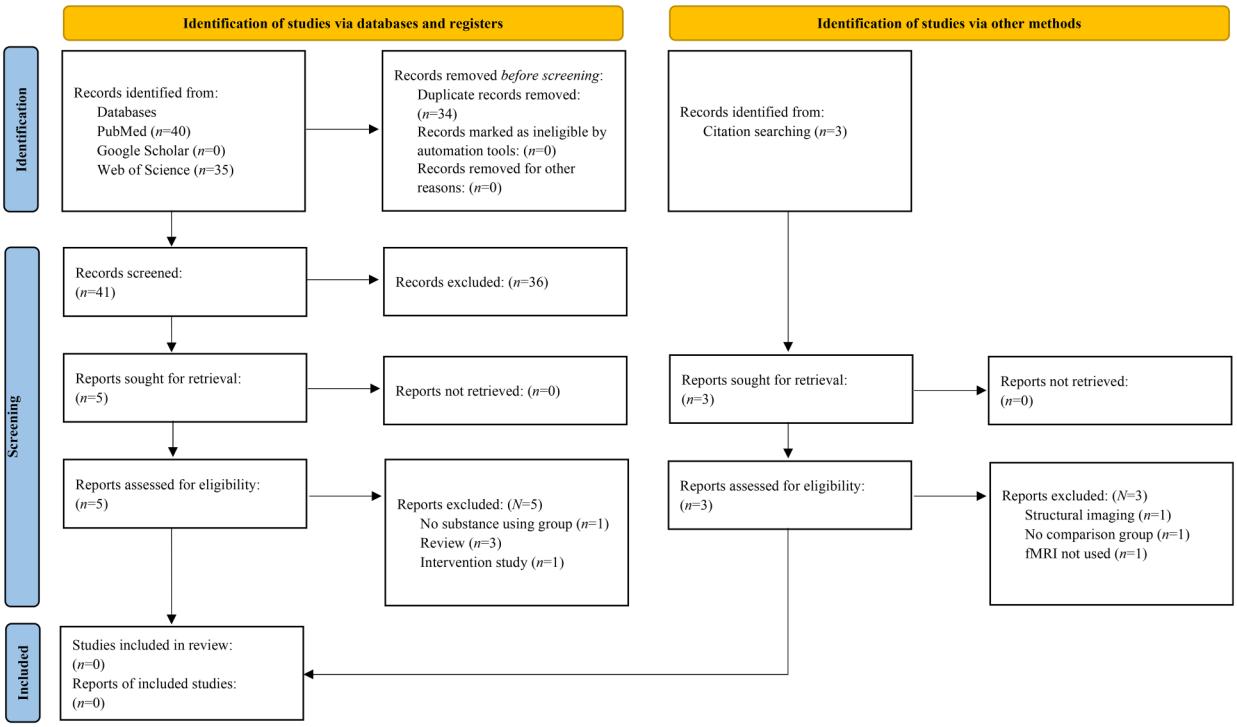

Figure 2. Flow diagram of literature search results from identification to inclusion for studies where trauma exposure is measured.

individuals that use tobacco, $n = 28$ controls), and one on cannabis ($n = 28$ individuals that use cannabis, $n = 23$ controls) as the substance of interest.

For studies with more than one comparison group,[38–49] we report any significant findings between the substance use group and one of the control groups. One study in the reward domain examined twin pairs discordant for cigarette smoking.[38] For this study, we chose the comparison of individuals who regularly smoked versus those who did not regularly smoke but not their co-twins. One study in the negative emotionality domain included three groups, ie, individuals with co-occurring alcohol use disorder (AUD)+Anxiety, individuals with AUD-Anxiety, and healthy controls.[39] To prevent introducing a confound of psychiatric illness in our review, we excluded the findings between the AUD + Anxiety group and the other two groups. Thus, we present only findings from the AUD-Anxiety versus healthy control groups.[39]

Refer to Figure 2 for the PRISMA diagram with a breakdown of the literature reviewed across all domains for the second literature search. No articles met the inclusion criteria to be included in the review. A breakdown of reasons we excluded articles is included in Figure 2.

Main Findings

A pictorial overview of the main findings can be found in Figure 3.

Reward Domain

See Table 1 for an overview of findings for this domain.

ACC. Greater (seven studies) and lesser (six studies) ACC activation in individuals using substances versus controls was observed. This discrepancy is likely dependent on the task used. Specifically, for cue-reactivity tasks, greater ACC was observed in individuals diagnosed with DSM-IV alcohol-dependence,[40] individuals who drank large amounts of alcohol,[41] individuals who used tobacco,[50] and individuals who used cannabis[51] than their respective control groups during the presentation of their substance cue of interest versus non-substance cue-related images. Conversely, during reward processing tasks, lesser ACC activation was observed in individuals diagnosed with either DSM-IV alcohol abuse or dependence,[52,53] individuals who experienced binge drinking episodes,[54] and individuals who used tobacco[43,55] than their respective control groups. However, see[56] as this study did not show this pattern. These findings highlight differential mechanisms of the ACC in response to passively viewing reward-related cues versus making conscious decisions regarding reward and loss. Given the ACC's role in evaluating reward value to maximize value and minimize punishment, individuals who use substances may be unable to correctly categorize rewarding stimuli as rewarding.

Regarding functional connectivity (FC), Strosche et al[42] found that individuals diagnosed with DSM-IV alcohol dependence exhibited decreased task-related FC between

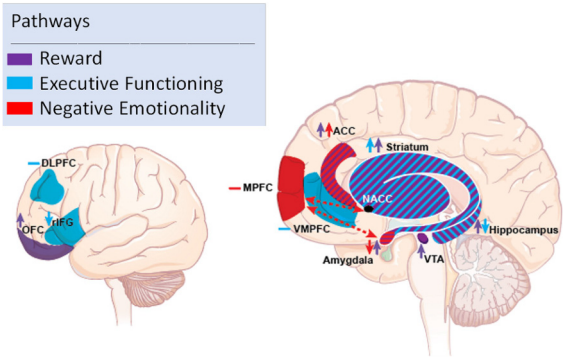

Figure 3. Overview of findings across each domain examined. Purple shading depicts activation in the reward domain, blue in the executive functioning (inhibition) domain, and red shading in the negative emotionality domain. Stripped shading highlights activation found in multiple domains for that respective region. Arrows depict greater or lesser activation in the respective region. Negative signs depict mixed activation found in the respective region. Abbreviations: DLPFC = dorsolateral prefrontal cortex; OFC = orbitofrontal cortex; rIFG = right inferior frontal gyrus; MPFC = medial prefrontal cortex; VMPFC = ventromedial prefrontal cortex; ACC = anterior cingulate cortex; NACC = nucleus accumbens; VTA = ventral tegmental area.

the ACC and insula and ACC and inferior frontal gryrus (IFG) while presenting alcohol-related cues than abstinent individuals.[42] During a feedback learning task, widespread greater FC in the dorsal ACC (dACC) and other target regions of interest, including the ACC, was found in individuals who use tobacco.[57] Lastly, one study found that during an unconscious presentation of tobacco smoking images versus the unconscious presentation of neutral images greater FC between the right amygdala and right ACC in individuals who use tobacco than those who did not use tobacco.[58]

Orbitofrontal cortex (OFC). Greater OFC reward-related activation was observed consistently across studies (eight studies), with a smaller portion showing lesser activation (two studies). In response to cue-reactivity tasks, individuals diagnosed with DSM-IV alcohol dependence,[40] individuals who transitioned from moderate to heavy drinking,[41] participants diagnosed with tobacco use disorder,[50] and individuals who used cannabis[51] exhibited greater OFC activation than their respective control groups during the presentation of their substance cue of interest versus non-substance cue-related images. During a monetary incentive delay task and feedback learning task, individuals who used tobacco exhibited greater OFC activation than controls.[43,57] During an attentional bias paradigm, individuals who used tobacco exhibited significantly lesser OFC activation than controls.[44] In response to an Iowa Gambling Task, individuals who used cannabis showed significantly greater activation in the right OFC during win versus loss trials than controls.[59]

Regarding FC, during an alcohol cue reactivity task, greater FC between the OFC and insula and lesser FC between the OFC and striatum was present in individuals diagnosed with DSM-IV alcohol dependence versus individuals abstaining from alcohol.[42] When responding to feedback learning tasks, individuals who used tobacco showed increased connectivity between the ACC and OFC versus those who did not use tobacco.[57]

VTA. In response to cue reactivity tasks, VTA activation is consistently greater in individuals with substance use than in controls (four studies), though see.[60] Individuals diagnosed with DSM-IV alcohol dependence,[42] individuals who used tobacco,[61] and individuals who used cannabis[51,62] exhibited greater activation in the VTA during the presentation of substance-related cues, such as images and odor versus neutral cues. In contrast, individuals at high risk for developing an AUD responding to alcohol cues during a Pavlovian instrumental transfer task exhibited decreased activation in the lateral prefrontal cortices than their low-risk counterparts.[60]

Striatum. Overall, individuals who used substances exhibited greater striatal activation than controls (17 studies), though there was variability (five studies showing lesser activation). During cue-reactivity tasks, individuals diagnosed with DSM-IV alcohol dependence,[40,42,63] individuals with nicotine dependence,[61,64] and individuals who used cannabis[43,51,62] exhibited greater striatal activation to their preferred substance or other rewarding stimuli than controls. Similarly, using monetary reward and anticipatory tasks,[46,65] card guessing tasks,[54,66] incentive processing tasks,[47,52] attentional bias paradigms,[44] and feedback learning tasks[57] increased striatal activation is present than controls. During an incentive processing task, individuals with an AUD diagnosis exhibited lower effective directional connectivity between the ACC to the ventral and dorsal striatum than controls without AUD.[52] A handful of studies have also found decreases in striatal activation during a Pavlovian instrumental transfer,[55] monetary reward,[43,47] card guessing,[38] and instrumental motivation tasks[67] in individuals using substances versus controls.

Amygdala. Greater (four studies) and lesser (two studies) amygdala activation were found in response to rewarding stimuli. In cue-reactivity tasks, individuals diagnosed with DSM-IV alcohol dependence,[42] individuals who used tobacco,[58,61] and individuals who used cannabis[51] exhibited greater amygdala activation to their respective preferred substance or other rewarding stimuli than controls. However, using a reward guessing game[54] and monetary incentive delay task,[43] individuals who used substances exhibited significantly decreased amygdala activation than individuals who did not use substances.

Hippocampus. In response to monetary reward tasks and cue reactivity tasks, greater hippocampal activation was found (seven studies), though lesser activation was also found (two studies). Specifically, individuals who used alcohol,[42,65] individuals diagnosed with nicotine dependence,[50,61,64] and individuals who used cannabis[47,51] exhibited significantly greater hippocampus activation than

Table 1. Reward studies.

Citation	Substance	Task Used	Experimental Group (n)	Age Mean (SD)	Percentage of Female Participants (%)	Control Group	Age Mean (SD)	Percentage of Female Participants (%)	OFC	ACC	VTA	Striatum	Hippocampus	Amygdala
van Holst, Clark, Veltman, van den Brink, Goudriaan, 2014	Alcohol	Monetary reward task (Expected value gained > expected value lost)	19	42.50 (10.40)	0.00%	19	40.40 10.70)	0.00%	-	-	-	↑	-	-
Dager et al., 2014	Alcohol	Cue-reactivity task (Alcohol > non-alcohol beverages)	16	18.69 (0.79)	50.00%	13	18.54 (0.88)	61.50%	↑	↑	-	-	-	-
Wiers et al., 2014	Alcohol	Cue-reactivity task (Approach alcohol > avoid alcohol) > (approach soft drink > avoid soft drink)	20	44.30 (7.98)	0.00%	17	42.12 (8.30)	0.00%	-	-	-	↑	-	-
Sjoerds et al., 2014	Alcohol	Cue-reactivity task (Alcohol > neutral images)	30	46.50 (8.50)	46.70%	15	46.80 (10.00)	26.7%	↑	↑	-	↑	-	-
Becker et al., 2017	Alcohol	Monetary reward task (Reward anticipation)	20	44.20 (10.30)	35.00%	20	44.90 (9.60)	45%	-	-	-	↑	↑	-
Crane et al., 2017	Alcohol	Reward guessing game (Win > loss)	27	24.00 (2.24)	44.00%	23	25.70 (2.95)	43%	-	↓	-	↑	↓	↓
Becker et al., 2017	Alcohol	Monetary reward anticipation task (Anticipation of monetary reward > anticipation of verbal reward)	31	45.4 (9.00)	22.60%	35	47.70 (8.90)	34%	-	-	-	↑	-	
Grodin et al., 2018	Alcohol	Reward incentive delay with shock task (High-threat alcohol-cue trials) (Low-threat alcohol-cue trials)	21	37.33 (13.49)	38.00%	21	35.62 (10.96)	43.00%	-	↑	-	↑	-	-
Chen et al, 2021	Alcohol	Pavlovian instrumental transfer task (Incongruent > congruent trials)	94	18.40 (0.20)	0.00%	97	18.40 (0.20)	0.00%	-	-	↓	↓	-	-
Arias et al., 2021	Alcohol	Number-guessing incentive processing task (Win trials)	78	29.00 (3.50)	45.00%	78	28.80 (3.70)	53.00%	-	↓	-	↑	-	-
Burnette et al., 2021	Alcohol	Balloon analogue risk task (Risk-taking trials)	16	31 (9.05)	31.00%	16	30.94 (10.39)	31.00%	-	↓	-	-	-	-
Strosche et al., 2021	Alcohol	Cue-reactivity task (Alcohol > neutral images)	13	47.00 (10.00)	39.00%	8	52.00 (12.00)	50.00%	↑↓	↓	↑	↑	↑	↑
Folco et al., 2021	Alcohol	Decision-making task (High-risk trials)	15	21.20 (2.08)	100.00%	16	20.25 (1.57)	100.00%	-	-	-	-	-	-
Hwang et al., 2022	Alcohol	Cue-reactivity task (Alcohol > neutral images)	20	31.40 (10.40)	50.00%	20	29.40 (9.30)	50.00%	-	-	-	-	-	-
van Hell et al., 2010	Cannabis	Monetary reward task (Anticipation of reward > anticipation of no reward)	14	24.00 (4.40)	1.00%	13	24.00 (2.70)	21.00%	-	-	-	↑↓	↑	–
Cousijn et al., 2013	Cannabis	Monetary decision-making	32	21.40 (2.30)	34.00%	41	22.20 (2.40)	37.00%	↑	-	-	-	–	-

(*continued*)

Table 1. Continued.

Citation	Substance	Task Used	Experimental Group (n)	Age Mean (SD)	Percentage of Female Participants (%)	Control Group	Age Mean (SD)	Percentage of Female Participants (%)	OFC	ACC	VTA	Striatum	Hippocampus	Amygdala
		task (Win > loss)												
Filbey et al., 2016	Cannabis	Cue-reactivity task (Cannabis cues > neutral object cues) (Cannabis cues > natural reward cues) (Fruit cues > neutral object cues)	53	30.66 (7.48)	37.70%	68	31.41 (10.20)	51.50%	↑	↑	↑	↑	↑	↑
Zhou et al., 2019	Cannabis	Cue-reactivity task (Cannabis cue > neutral cue)	18	22.94 (2.71)	0.00%	44	23.20 (4.32)	0.00%	-	-	-	↑	-	-
Kleinhans et al., 2020	Cannabis	Cue-reactivity task (Cannabis odor > baseline) (Cannabis cue > baseline)	25	26.17 (4.15)	48.00%	25	26.21 (5.05)	48.00%	-	-	↑	↑	-	-
Yalachkov, Kaiser, & Naumer, 2009	Tobacco	Cue-reactivity task (Smoking-related > control images)	15	27.10 (3.80)	60.00%	15	28.70 (6.80)	60.00%	-	-	-	↑	↑	-
de Ruiter et al., 2009	Tobacco	Probabilistic reversal-learning task (Monetary gain trials)(Monetary loss trials)	19	34.80 (9.80)	0.00%	19	34.10 (9.30)	0.00%	-	-	-	-	-	-
Zhang et al., 2009	Tobacco	Backward masking paradigm (Smoking-related > neutral images)	10	25.10 (1.07)	0.00%	10	23.80 (0.81)	0.00%	-	↑	-	-	-	↑
Bühler et al., 2010	Tobacco	Instrumental motivation task (Monetary reward > cigarette reward)	21	28.00 (4.30)	NR	21	25.70 (6.10)	NR	-	-	-	↓	-	-
Nestor et al., 2011	Tobacco	Attentional bias task (Neutral, evocative, and smoking trials)	21	24.30 (1.20)	46.00%	13	23.60 (1.30)	62.00%	↓	↓	-	↑	-	-
Janes et al., 2012	Tobacco	Cue-reactivity task (Smoking > neutral cues)	13	39.9 (10.10)	100.00%	16	42.40 (10.80)	100.00%	-	-	↑	↑	↑	↑
Lessov-Schlagger et al., 2013	Tobacco	Number-guessing task Time courses for each condition (reward, punishment, neutral)	15	28.70 (3.27)	100.00%	15	28.70 (3.27)	100.00%	-	-	-	↓	-	-
Nestor et al., 2018	Tobacco	Monetary incentive delay task (Loss anticipation trials) (Gain anticipation trials)	15	23.30 (1.20)	60.00%	15	23.80 (1.20)	47.00%	↑	-	-	↓	↓	↓
Duehlmeyer & Hester, 2019	Tobacco	Divergent value learning and errors task (Future feedback performance [corrected error, repeated error])	23	25.48	35.00%	23	24.74	57.00%	-	-	-	-	-	-

(*continued*)

Table 1. Continued.

Citation	Substance	Task Used	Experimental Group (n)	Age Mean (SD)	Percentage of Female Participants (%)	Control Group	Age Mean (SD)	Percentage of Female Participants (%)	OFC	ACC	VTA	Striatum	Hippocampus	Amygdala
		(Monetary feedback magnitude [$0.05, $0.50])												
Lawn et al., 2020	Tobacco	Value-based decision-making task (Purchase cigarette bundle > do not purchase cigarette bundle)	19	29.5 (10.70)	16.00%	19	22.7 (4.40)	32.00%	-	↓	-	-	-	-
Kunas et al., 2022	Tobacco	Cue-reactivity task (Drug-related-positive cues)	38	35.18 (10.57)	55.26%	42	32.36 (10.97)	73.81%	↑	↑	-	-	↑	-
Duehlmeyer et al., 2022	Tobacco	Feedback learning task (Feedback conditions [-$0.50, -$0.05, +$0.50, + 0.05]) (All epochs [recall, feedback, and re-encoding)	23	25.48	35.00%	23	24.74	57.00%	↑	↑	-	↑	-	-

Notes. Abbreviations: SD = standard deviation; NR = not reported; OFC = orbitofrontal cortex; ACC = anterior cingulate cortex; VTA = ventral tegmental area

Table 2. Negative emotionality studies.

Citation	Substance	Task Used	Experimental Group (n)	Age Mean (SD)	Percentage of Female Participants (%)	Control Group (n)	Age Mean (SD)	Percentage of Female Participants (%)	OFC	mPFC	ACC	Hippocampus	Amygdala
Brown-Rice et al., 2018	Alcohol	Rank Emotion Task (Negative > positive conditions)	21	Range: 18-25	57.89%	23	Range: 19-24	63.64%	-	↑	-	-	-
MacIlvane et al., 2020	Alcohol	Emotional face-matching task (Fearful Faces > shapes) (Fearful faces > neutral faces)	39	39.90 (12.59)	28.20%	103	36.08 (11.14)	55.34%	-	-	-	-	-
Gorka et al., 2020a	Alcohol	Threat-of-shock startle task (Unpredictable shock with countdown > no shock with countdown) (Predictable shock with countdown > no shock with countdown)	38	23.80 (3.00)	42.10%	27	24.30 (2.80)	44.40%	-	-	↑	-	-
Gorka et al., 2020b	Alcohol	Threat-of-shock startle task (Unpredictable threat > no threat) (Predictable threat > no threat)	33	23.60 (2.80)	39.40%	24	24.00 (2.60)	54.20%	-	↓	-	-	↓
Zhao et al., 2020	Cannabis	Montreal imaging stress task (Stress > no stress condition)	28	25.54 (5.11)	0.00%	23	24.57 (3.55)	0.00%	-	-	-	-	-
Onur et al., 2012	Tobacco	Modified face perception task (All faces > houses) (Fearful faces > neutral faces)	28	26.32 (2.79)	50.00%	28	26.88 (2.44)	50.00%	-	-	-	-	-

Notes. Abbreviations: SD = standard deviation; OFC = orbitofrontal cortex; mPFC = medial prefrontal cortex; ACC = anterior cingulate cortex.

Table 3. Executive functioning (inhibition) studies.

Citation	Substance	Task Used	Experimental Group (n)	Age Mean (SD)	Percentage of Female Participants (%)	Control Group (n)	Age Mean (SD)	Percentage of Female Participants (%)	vmPFC	IFG	Striatum	dlPFC	Hippocampus
Ahmadi et al., 2013	Alcohol	Go/No-Go task (No-go correct rejections)	35	18.97 (0.45)	65.80%	56	18.80 (0.97)	44.70%	↓	-	↓	-	↓
Ames et al., 2014	Alcohol	Go/No-Go task (No-go trials)	21	20.19 (1.40)	52.00%	20	20.75 (1.07)	65.00%	↑	-	-	↑	-
Campanella et al., 2017	Alcohol	Go/No-Go task (Correct No-go trials) (all correct trials)	19	24.70 (3.00)	63.15%	17	25.80 (4.20)	58.82%	-	-	↑	-	-
Hu et al., 2016	Alcohol	Stop signal reaction time task (Stop success > Go success)	57	29.10 (9.60)	39.00%	57	31.50 (11.80)	46.00%	↓	-	-	-	-
Alderson et al., 2021	Alcohol	Go/No-Go task (Error No-go > Correct No-go)	19	23.50 (3.10)	57.00%	18	25.60 (4.10)	50.00%	↑	-	-	-	-
Nestor et al., 2011	Tobacco	Go/No-Go task (Stop trials) (Error trials)	10	23.00 (1.00)	50.00%	13	23.60 (1.30)	62.00%	↓	↓	-	↓	↓
de Ruiter et al., 2012	Tobacco	Stop signal task (Successful stop > control) (Failed stop > control) (Successful inhibition > control) (Failed inhibition > control)	18	33.80 (9.10)	0.00%	17	34.70 (9.70)	0.00%	-	↓	-	-	-
Clewett et al., 2014	Tobacco	Delay discounting task (Steeply discounted expected rewards)	39	35.90 (8.70)	33.30%	33	30.10 (7.20)	47.00%	-	-	-	-	-
Akkermans et al., 2018	Tobacco	Go/No-Go task (Go correct > No-Go correct) (No-Go correct > Go correct)	25	22.56 (2.84)	28.00%	23	21.74 (1.82)	39.00%	-	-	↑	-	-

Notes. Abbreviations: SD = standard deviation; vmPFC = ventromedial prefrontal cortex; IFG = inferior frontal gyrus; dlPFC = dorsolateral prefrontal cortex.

individuals who did not use. During a reward guessing game[54] and a monetary incentive delay task,[43] decreased hippocampal activation was found in individuals who used substances compared to individuals who did not use them.

Summary. Mixed findings appeared in the ACC; greater ACC activation was present in individuals who used substances when passively viewing substance-related cues. However, lesser ACC activation tended to be found when participants made conscious decisions while completing reward-processing tasks. This finding could be explained by the inability of individuals who use substances to acknowledge rewarding stimuli as rewarding. In response to reward tasks, individuals who used substances tended to show significantly greater OFC, VTA, amygdala, and hippocampal activation than controls who did not use substances. FC analyses highlight alterations in the ACC and OFC, highlighting FC alterations in more cortical regions than subcortical.

Negative Emotionality Domain

See Table 2 for an overview of findings from this domain.

Medial Prefrontal Cortex (mPFC). One study found greater middle frontal gyrus (MFG) activation in individuals who exhibited hazardous drinking patterns while presenting negative stimuli than individuals who did not exhibit hazardous drinking patterns.[68] Regarding FC findings, less mPFC-amygdala FC was associated with more binge episodes within the past 60 days and a younger age of AUD onset.[69]

ACC. One study found greater dACC reactivity during uncertain and predictable threats in individuals diagnosed with AUD than those without AUD.[69]

Amygdala. One study found no group differences between individuals with AUD and anxiety and individuals diagnosed with AUD only or healthy controls when examining fearful faces versus shapes or between individuals who use tobacco compared to individuals who do not smoke tobacco when examining emotional facial expressions.[70]

Summary. Greater MFG,[68] lesser mPFC activation, and decreased amygdala-mPFC FC during unexpected threats were associated with more binge episodes in individuals who experience binge drinking episodes.[69] These findings follow studies suggesting lesser FC would suggest deficient control of amygdala activation by the mPFC. The finding of greater dACC activation in individuals diagnosed with AUD in response to threat than controls is also in line with previous data on the role of the dACC in contributing to increased anxious states in individuals with AUD.[69] One study found differences in the ACC in individuals diagnosed with AUD versus controls; more studies are needed to clarify the role of the ACC and other regions implicated in threat in individuals who use substances. This domain is especially important to explore as the 'self-medication' hypothesis has proposed extensive use of substances to alleviate anxiety or depression symptoms, leading to the ultimate development of a substance use problem.

Inhibition Domain

See Table 3 for an overview of findings for this domain.

ACC. In response to inhibition tasks, greater (two studies) and lesser (three studies) activation has been found in individuals who use substances than controls. When completing the Go/No-Go task, individuals who drank heavily,[71] socially drank,[72] and previously used tobacco[44] exhibited significantly lower ACC activation than controls. However, the opposite activation pattern has been found using the same task. Specifically, individuals who drank heavily exhibited stronger activation in the right dorsolateral PFC (dlPFC) and dACC than individuals who drank light during No-Go trials.[73] These discrepant findings are likely caused by differences in contrasts examined and, therefore, differences in underlying neural processes. Specifically, studies that found lower ACC activation examined the correct inhibition responses versus errors. In contrast, studies that showed greater activation were found using the opposite contrast, error inhibition responses versus correct.

Individuals who experienced binge drinking episodes exhibited greater activation than individuals who drank light in the rACC and increased FC between the rACC and right lateral frontal cortex during the error No-Go > Correct No-Go responses.[74]

IFG. Two studies showed reduced rIFG activation in individuals who use tobacco. Specifically, significantly lesser activation was found in the IFG during the Go/No-Go task[44] and the Stop Signal Task[48] than in controls.

dlPFC. Findings of inhibition-related dlPFC activation in substance use were mixed, with one study finding greater and one finding lesser activation. Significantly greater dlPFC activation during the go/no-go task was observed in individuals who drank heavily versus individuals who drank light.[73] Still, there was less dlPFC activation in individuals who use tobacco than in controls, and individuals who used to smoke tobacco were observed using the same task.[44]

Striatum. Studies showed greater (two studies) and lesser (one study) activation in the striatum during inhibition-related tasks in individuals who use substances. During failed inhibition trials, one study found greater left caudate nucleus activation in individuals who drank heavily versus individuals who drank light,[75] while, during No-Go correct trials, individuals who drank heavily exhibited decreased activation in the putamen than individuals who drank light.[71] This discrepancy can likely be caused by the difference in contrast examined.

Greater FC between the striatum (anterior putamen) and insula was found in individuals who used tobacco than in those who did not.[76]

Hippocampus. Two studies show lower hippocampal activation during inhibition. Lesser hippocampal activation during No-Go correct trials in individuals who drank heavily versus individuals who drank light[71] and significantly lesser parahippocampal gyrus activation in both individuals

who use tobacco and individuals who previously used tobacco versus controls during Stop trials[44] was observed.

Summary. During response inhibition, mixed findings were present in the ACC, striatum, and dlPFC, while consistently lesser activation was observed in the IFG and hippocampus. The IFG is especially important in inhibitory processes; thus, the finding of lesser rIFG activation provides a biomarker for unsuccessful inhibition in individuals using substances, though replication of this finding is needed. It is important to highlight that the type of inhibition assessed during the tasks reviewed here are largely motor inhibition tasks and do not measure more self-control-related processes underlying impulsivity.

Discussion

This review systematically synthesized neuroimaging studies focusing on three domains that may contribute to the overlapping mechanisms of SUD and PTSD—reward salience, negative emotionality, and executive function (response inhibition). We focused on samples of individuals who use substances where trauma exposure is not measured and studies that explicitly measure trauma exposure, enabling us to draw conclusions from and identify knowledge gaps for each population. Our findings suggest altered activation and FC in reward, inhibition, and negative emotionality neural circuits in currently using, dependent on substances, or clinically diagnosed with SUD than controls. Notably, no studies on trauma-exposed individuals using, dependent on, or clinically diagnosed with SUD met the criteria for our systematic review. The implications of these findings are discussed below.

Reward Domain

Overall, the studies reviewed showed greater activation in individuals who use substances versus controls across many brain regions important in the mesocorticolimbic pathway, including the OFC, VTA, amygdala, and hippocampus, when using reward-related tasks such as cue-reactivity and monetary incentive tasks.

An increase in VTA and striatal activation during the presentation of cue-related activation is not surprising, given that the VTA is responsible for releasing dopamine to the striatum in response to rewarding stimuli.[77] However, even in individuals with substance use dependence, there was still greater activation in these areas compared to individuals without substance use dependence to cue-related stimuli. This was surprising given previous literature that suggests individuals dependent on a substance no longer exhibit similar increases in dopaminergic initiation given the tolerance created for the substance.[9] We excluded intervention studies that gave participants a substance inside the scanner; thus, the contextual cues associated with that substance rather than the actual substance could provide a greater release of dopamine-producing a rewarding effect. We did find greater activation in the hippocampus in individuals who use substances versus controls, providing evidence of the importance of context cue processing during reward processing. Thus, these findings highlight that activation in response to viewing reward-related stimuli leads to greater activation of brain regions underlying reward even during dependence.

The increased activation in the VTA and striatal findings may suggest that when passively viewing rewards without the ability to receive the reward leads to an increase in reward-related activation, whereas actively receiving the reward or consciously making decisions with outcomes that will directly affect the participant may lead to deficient regulation of reward in the VTA, striatum, and ACC.

Negative Emotionality Domain

The negative emotionality domain, whose phenotypical expression is related to the mesolimbic domain of the brain, encompasses the mPFC, ACC, and amygdala. Only 6 studies were eligible to be included in the review. Regardless, these results highlight greater dACC and lesser mPFC activation in individuals with hazardous drinking patterns and AUD compared to controls.

The dACC is important in the acquisition of conditioned fear. Thus, greater activation in the dACC could suggest that individuals who use substances have altered appraisal and expression of conditioned fear than controls. Interestingly, one study found greater MFG activation in response to negative images in individuals with hazardous drinking patterns versus individuals who do not exhibit hazardous drinking patterns.[68] This finding is interesting, given the regulatory role of the MFG in responding to potentially threatening stimuli. However, the MFG is potentially trying to hyper-regulate regions responsible for fear expression (ie, the amygdala), leading to maladaptive responses.

Inhibition Domain

Overall, studies found lesser activation in the IFG and hippocampus. In contrast, mixed findings in activation were present in the ACC, striatum, and dlPFC in individuals who used substances versus controls.

Given its important role in executing successful response inhibition, the findings of lesser IFG in individuals who use tobacco could correspond with the behavioral deficits seen in inhibiting their urge to use substances, even when the substance is causing functional difficulties in the person's life. Deficiencies in the brain regions responsible for inhibition may lead to impulsive behavior associated with initiating and maintaining substance use.[78] More studies are needed to determine better the role of the ACC, striatum, and dlPFC in inhibitory processes.

Trauma-Exposed Samples

No studies were identified that examined functional MRI correlates of reward salience, negative emotionality, or inhibition in substance use samples with trauma exposure that met the criteria of our PRISMA-guided systematic review. Given that trauma is a risk factor for the development of substance use and SUD, as well as the large co-occurrence of PTSD and SUD, it is likely that our sample of individuals who use substances has some proportion who were un-assessed trauma-exposed individuals. Therefore, studies are needed to examine the intersection of trauma history with functional correlates of reward salience, inhibition (or executive function), and negative emotionality in individuals who use substances. Determining how an individual responds to a stressor and how trauma-related factors may interact with neurobiological mechanisms to influence SU may facilitate screening individuals at risk and developing targeted clinical interventions to mitigate the escalation of substance use.

Limitations and Future Directions

There are limitations of the literature reviewed. First, this review highlights a lack of studies that have systematically measured trauma exposure in individuals who use substances when examining reward, negative emotionality, and inhibition neurocircuitry. We could not identify studies conducted in trauma-exposed samples; however, as noted above, it is plausible that participants in the studies where trauma exposure was not measured did indeed experience trauma, but trauma exposure was not assessed in these studies. It will be imperative to measure trauma exposure moving forward in studies using samples who use substances to start understanding the potential neural mechanisms associated with trauma that contribute to the development of substance use or vice versa. Second, while many studies examined neural correlates of reward-related neurocircuitry in SUDs, neuroimaging studies are only beginning to more thoroughly explore negative emotionality and negative emotionality in individuals who use substances[79-81] Future studies should extend this research to utilize tasks focusing on these domains to determine whether alterations are associated with substance use maintenance and development. Third of the studies reviewed, participants with varying levels of substance use were combined, including individuals who occasionally use, those who use heavily, and those diagnosed with a SUD. More studies should focus on each level of the substance use cycle to understand the neural correlates of early use, transitioning to heavy use, and later disorder. Lastly, many studies reviewed contained small sample sizes (n's < 100 per group). In the future, studies utilizing bigger samples should be published to increase the power to determine effects.

There are also limitations related to our systematic review. First, our systematic review focuses on alcohol, tobacco, and cannabis use, given that these substances have been reported most in trauma studies.[37] Other substances are important to explore, such as cocaine, heroin, and fentanyl. In addition, less research has been done on developing substance use post-trauma. Because our literature searches showed no studies examining trauma, we categorized the studies as not having measured trauma exposure. However, given that trauma exposure is a common risk factor for developing a SUD, such a sample is unlikely to be entirely unexposed to trauma. Therefore, the conclusions related to this sample should be interpreted with caution. It is important to note that the studies without trauma exposure do not mean the participants in these studies were not trauma-exposed, only that their trauma was not directly measured within the confines of the study. More neuroimaging studies should investigate the neural underpinnings associated with susceptibility to developing substance use problems post-trauma. Lastly, causality was not addressed in this review. It will be imperative to discover whether these findings result from using these substances or make an individual more prone to developing substance use issues. To answer this important question, longitudinal and twin samples should be used in the future.

Conclusion

This review systematically synthesizes neuroimaging studies focusing on three domains associated with substance use and may contribute to the overlapping mechanisms of SUD and PTSD—reward, negative emotionality and inhibition. More definitive research on individuals using substances, especially those with trauma exposure, and how these responses may contribute to the development and maintenance of substance use is needed. Consistent with existing literature, we have highlighted deficits in each domain, specifically greater activation in regions involved in reward processing, greater and lesser activation in regions involved in negative emotionality processes, lesser activation in regions involved in inhibition processing. Additionally, we propose that future studies should emphasize executive function and negative emotionality processes, investigate the role of trauma-related factors, and use longitudinal designs to better understand the underlying development of neurobiological alterations, providing mechanistic targets for preventative measures and treatment outcomes.

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Supplemental Material

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