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Real-time fMRI-based neurofeedback to restore brain function in substance use disorders: A systematic review of the literature

Ethan Murphy [a], Govinda Poudel [b], Saampras Ganesan [c,h,i], Chao Suo [a,d], Victoria Manning [e,f], Emillie Beyer [a], Adam Clemente [a], Bradford A. Moffat [g], Andrew Zalesky [c,h], Valentina Lorenzetti [a,*]

[a] Neuroscience of Addiction and Mental Health Program, Healthy Brain and Mind Research Centre, School of Behavioral and Health Sciences, Faculty of Health, Australian Catholic University, Australia
[b] Mary MacKillop Institute for Health Research, Australian Catholic University, Australia
[c] Department of Psychiatry, Melbourne Medical School, The University of Melbourne, Australia
[d] BrainPark, Turner Institute for Brain and Mental Health, Monash University, Clayton, Australia
[e] Monash Addiction Research Centre, Eastern Health Clinical School, Monash University, Clayton, Australia
[f] Turning Point, Eastern Health, Melbourne, Victoria, Australia
[g] Melbourne Brain Centre Imaging Unit, Department of Radiology, The University of Melbourne, Australia
[h] Department of Biomedical Engineering, The University of Melbourne, Australia
[i] Contemplative Studies Centre, Melbourne School of Psychological Sciences, The University of Melbourne, Australia

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ABSTRACT

Introduction: Real-time functional magnetic resonance based-neurofeedback (fMRI-neurofeedback) is a neuromodulation tool where individuals self-modulate brain function based on real-time feedback of their brain activity. fMRI-neurofeedback has been used to target brain dysfunction in substance use disorders (SUDs) and to reduce craving, but a systematic synthesis of up-to-date literature is lacking.
Method: Following PRISMA guidelines, we conducted a systematic review of all the literature that examined the effects of fMRI-neurofeedback on individuals with regular psychoactive substance use (PROSPERO pre-registration = CRD42023401137).
Results: The literature included 16 studies comprising 446 participants with SUDs involving alcohol, tobacco, and cocaine. There is consistent *between-condition* (e.g., fMRI-neurofeedback versus control), less consistent *pre-to-post* fMRI-neurofeedback, and little *intervention-by-time* effects on brain function in prefrontal-striatal regions and craving.
Conclusion: The evidence for changes in brain function/craving was early and inconsistent. More rigorous experiments including repeated measure designs with placebo control conditions, are required to confirm the efficacy of fMRI-neurofeedback in reducing brain alterations and craving in SUDs.

1. Introduction

Substance use disorders (SUDs) are highly prevalent globally, with an estimated 164 million people having an SUD in 2016 (Degenhardt et al., 2018). Further, SUDs accounted for almost 65,000 years of life lost due to premature death in 2019 alone (Castelpietra et al., 2022). SUDs can be characterised by relapse rates ranging from 40-to-60 % (Brandon et al., 2007) with intervention dropout rates ranging from 25 %-to-54 % (Lappan et al., 2020), and failed attempts to cut down/quit using addictive substances despite experiencing significant psychosocial harms (American Psychiatric Association, 2013). These harms include the experience of intense craving to use (Hasin et al., 2013), greater symptoms and/or diagnosis of mental ill health (e.g., anxiety, depression, psychosis; Lai et al., 2015), suicidality (Bohnert et al., 2017), and a four-fold increased risk of general mortality (Chang et al., 2010).

The adverse outcomes of SUDs have been postulated to partly arise from neurobiological alterations as per prominent neuroscientific theories of addiction (Koob and Volkow, 2016). Consistently, mounting evidence from functional magnetic resonance imaging (fMRI) studies confirms altered brain function (e.g., activity and/or functional connectivity) in

* Corresponding author.
E-mail address: valentina.lorenzetti@gmail.com (V. Lorenzetti).

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SUDs in regions underlying cognitive processes characteristic of addictive behaviour. These regions support decision-making and craving (e.g., anterior cingulate cortex [ACC]), stress (e.g., amygdala), disinhibition (e.g., prefrontal cortex [PFC]), interoception (e.g., insula), and reward processing [e.g., striatum] (Koob and Volkow, 2016). Given the neurobiological underpinning of SUDs, novel brain-based interventions that directly target brain alterations in SUDs have been called for (Joutsa et al., 2022; Kozak et al., 2019; Volkow and Boyle, 2018). Although this has been attempted over the last few decades, one such tool that has become more prevalent in recent years is real-time fMRI-based-neurofeedback (henceforth 'fMRI-neurofeedback').

fMRI-neurofeedback is a non-invasive neuromodulation technique where people receive real-time feedback on their brain function via a brain-computer interface (e.g., a digital thermometer, see Fig. 1). By presenting information on brain function, fMRI-neurofeedback enables the real-time regulation of people's own brain function in deep brain nuclei often implicated in psychopathology (e.g., ACC, nucleus accumbens; Sitaram et al., 2017). Thus, fMRI-neurofeedback can target various disease processes, including but not limited to reduced craving in SUDs (Karch et al., 2015, 2019; Kirsch et al., 2016), improved motor function in Parkinson's Disease (Tinaz et al., 2022), increased mood in depression (Pindi et al., 2022), and greater response inhibition in Attention-Deficit Hyperactivity Disorder (Alegria et al., 2017).

One narrative review has been published suggesting that fMRI-neurofeedback can reduce brain alterations and craving in SUDs (Martz et al., 2020), which is promising given that craving is a significant predictor of substance relapse (Sliedrecht et al., 2019; Vafaie and Kober, 2022). However, the evidence on fMRI-neurofeedback in SUDs has not been systematically summarised and the field has evolved in the years since the previous narrative review. Therefore, it remains unclear whether there is consistent evidence for the effects of fMRI-neurofeedback on brain function, craving, and substance use (i.e., 'neurobehaviour') in SUDs. The primary aim of this review is to address this evidence gap by systematically synthesising the literature on fMRI-neurofeedback-related neurobehavioural changes in SUDs. Second, we aimed to systematically summarise the evidence on the association between fMRI-neurofeedback-related brain functional changes, craving, and substance use. Finally, we aimed to evaluate the methodological quality of the literature to date.

2. Methods

2.1. Protocol and registration

This review was pre-registered on the International Prospective Register of Systematic Reviews ([PROSPERO], submitted [21/02/2023], approved [22/02/2023]; ID: CRD42023401137). Each component of the review has been performed in accordance with the latest Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021).

2.2. Literature search

A comprehensive systematic search of the literature was undertaken to identify studies investigating fMRI-neurofeedback in addiction published until February 26, 2024. Four databases were searched: MEDLINE (EBSCOhost), PsycINFO (EBSCOhost), Scopus, and PubMed. The search strategy consisted of three primary concepts: i) addiction (both behavioural addiction and substance use), ii) functional neuroimaging, and iii) fMRI-neurofeedback. The detailed search strategy is described in the supplementary (Supplementary Tables 1–4).

2.3. Study selection

The PRISMA flowchart in Fig. 2 describes the overall screening process carried out using the systematic review tool, Covidence (www.covidence.org). The searches retrieved a total of 978 studies, of which 299 duplicates were immediately removed. The titles and abstracts of the remaining 679 studies were independently screened by two researchers (EM and EB) against the following inclusion and exclusion criteria: i) written in the English language, ii) examined human participants, iii) peer-reviewed and empirical, iv) use of a fMRI-neurofeedback paradigm, and v) the regular use of a psychoactive substance or participation in non-substance-related addictive behaviour, as defined by each study's protocol. The exclusion criteria were i) use of a neurofeedback technique other than fMRI, ii) non-empirical work, iii) meta-analyses or reviews, and iv) non-human sample. Seventeen articles were eligible for full-text screening carried out by EM and EB. Disagreements between screeners arose on one occasion and were resolved following discussion with VL. The study was subsequently removed due

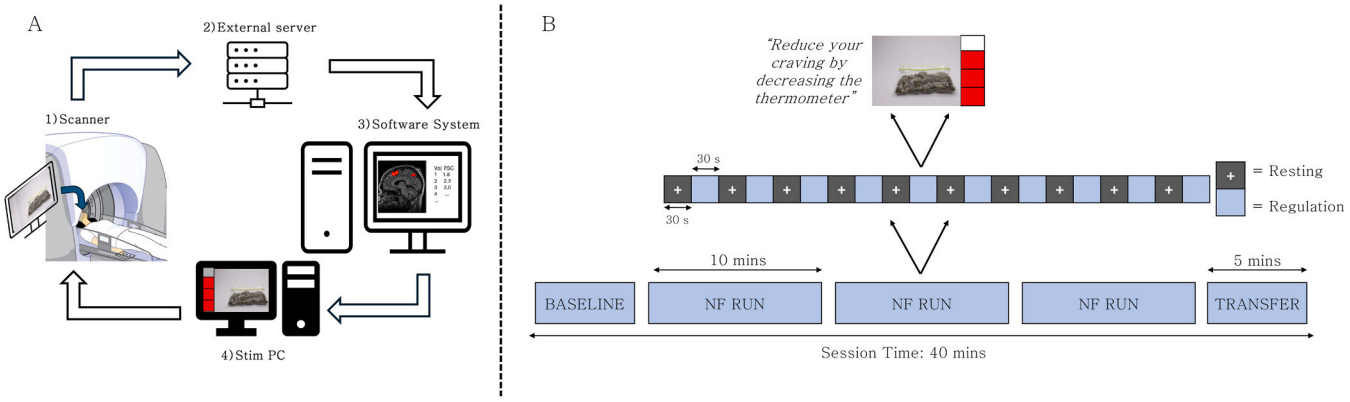


Fig. 1. Schematic of a common SUD fMRI-neurofeedback experimental design for a session scan time lasting 40 minutes (mins). A). Inside the scanner, the BOLD signal is collected from participants while they view substance-related stimuli. This fMRI data is passed to an external server, and then onto a software system (e.g., Turbo-BrainVoyager [TBV]) that processes the fMRI data in real-time. The signal from the relevant regions (e.g., percentage signal change [PSC]) is sent to the Stimulation (Stim) PC and presented to participants in the form of visual feedback (e.g., thermometer). B). The fMRI-neurofeedback process can be disaggregated into three distinct phases: (i) training run, where participants perform cue-induced craving to identify the personalised brain region to be targeted by fMRI-neurofeedback; (ii) fMRI-neurofeedback runs (NF), where participants change their brain function in real-time while attempting to down-regulate cue-induced craving, interspersed with rest blocks (e.g., fixation cross); (iii) transfer run, where participants perform cue-induced craving without the interface to investigate if they have learned to change their own brain function.

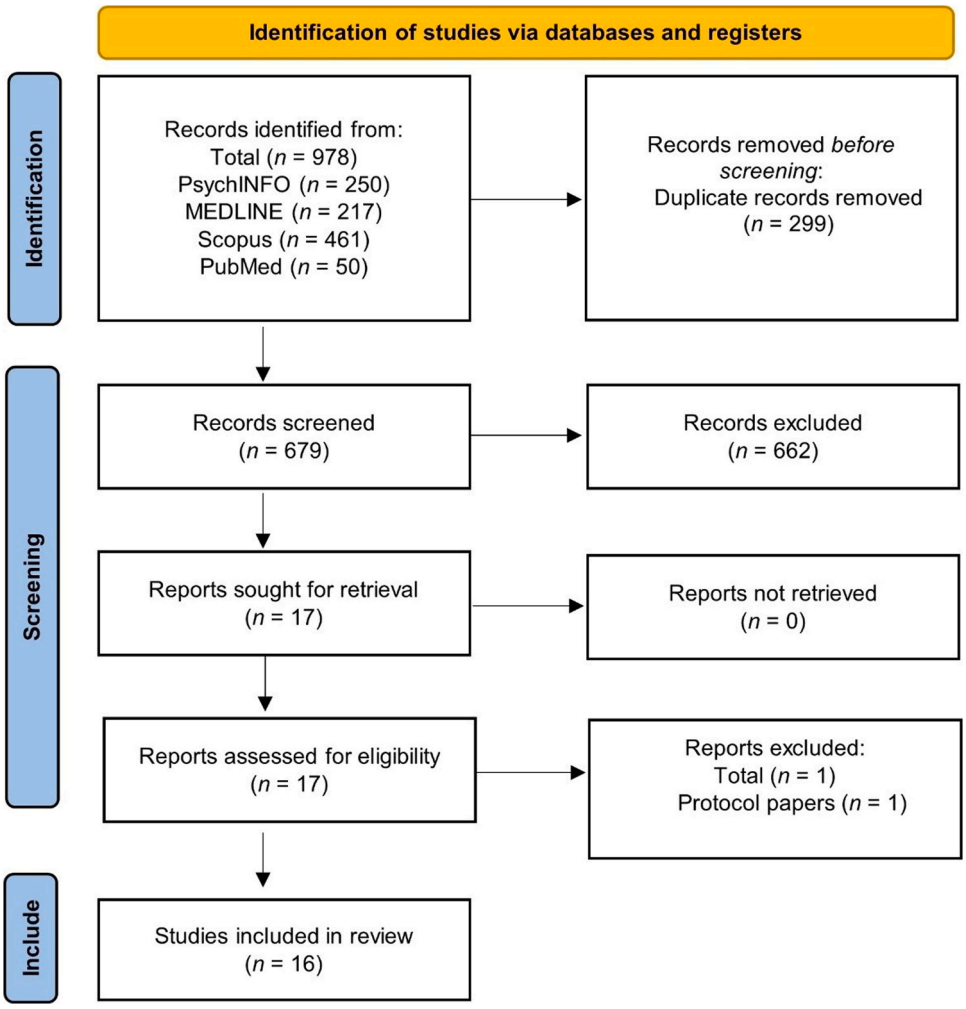


Fig. 2. PRISMA flowchart outlining the systematic study selection.

to its non-empirical nature. A total of 16 studies were selected for inclusion in this review. Full-text articles were cross-referenced for additional relevant studies; however, no new studies were identified.

2.4. Data extraction

Data from the included 16 studies were systematically extracted and inputted into Excel spreadsheets. The extracted data was categorised into three domains relating to i) study and participant characteristics (e.

Table 1
Overview of key baseline demographics and substance use characteristics of the reviewed literature.

Author, year	Substance	Sample size, N (female)		Mean age, years (st.dev)		Substance use, mean (st. dev)	
		SUD	Controls	SUD	Controls	Dosage	Duration, years
Sanader Vukadinovic, 2024	alcohol	16 (_)	_	_	_	_	_
Fede, 2023	alcohol	30 (12)	_	41 (_)	_	_	_
Chung, 2023	tobacco	44 (10)	_	27 (8)	_	15 cig/day (7)	10 (8)
Karch, 2022	alcohol	48 (7)	_	46 (12)	_	_	_
Subramanian, 2021	alcohol	52 (16)	_	46 (10)	_	32 drink/day (8)	_
Kim, 2021	tobacco	14 (0)	_	26 (2)	_	17 cig/day (3)	7 (2)
Rana, 2020	tobacco	4 (0)	_	_	_	20 cig/day (_)	_
Karch, 2019	tobacco	36 (11)	_	44 (12)	_	20 cig/day (6)	26 (14)
Kirschner, 2018	cocaine	22 (8)	28 (14)	30 (7)	29 (8)	0.3 g/day (0.3)	5 (5)
Kirsch, 2016	alcohol	38 (9)	_	24 (3)	_	_	_
Hartwell, 2016	tobacco	44 (16)	_	35 (11)	_	19 cig/day (6)	18 (10)
Karch, 2015	alcohol	13 (_)	14 (_)	_	_	_	_
Kim, 2015	tobacco	14 (0)	_	26 (2)	_	17 cig/day (3)	7 (2)
Canterterberry, 2013	tobacco	9 (1)	_	33 (13)	_	13 cig/day (4)	_
Hanlon, 2013	tobacco	9 (1)	_	_	_	_	_
Li, 2013	tobacco	10 (7)	_	29 (11)	_	15 cig/day (5)	_

Acronyms: cig, cigarette; *N*, number; SUD, substance use disorder; st.dev, standard deviation. '_', not investigated/not applicable/ not provided.

g., author, year of publication, substance use characteristics; Table 1), ii) experimental and methodological variables (e.g., study design, fMRI analysis, fMRI-neurofeedback-related parameters), and iii) results (e.g., brain functional changes related to fMRI-neurofeedback, changes in behaviour [e.g., craving, substance use] and the association between brain functional changes and behaviour; Tables 2–4).

Specifically, neurobehavioural results from all studies were grouped as a function of the design used to measure the change in brain function during fMRI-neurofeedback: i) changes *pre-to-post* fMRI-neurofeedback intervention, ii) changes between *fMRI-neurofeedback and active/passive/no control conditions (i.e., control conditions)*, and iii) *intervention-by-time* effects (e.g., neurofeedback groups compared after the intervention). The ratio of studies that satisfied a specific criterion (e.g., effects on brain activity between fMRI-neurofeedback and control *conditions*) was calculated by dividing the number of studies with significant results in that criterion by the number of studies investigating that criterion.

2.5. Risk of bias and quality assessment

The risk of bias of the reviewed literature was assessed using two tools (each used independently) from the National Institutes of Health (NIH), National Heart, Lung, and Blood Institute: *Quality Assessment Tool for Observational Cohort and the Cross-Sectional Studies* (Supplementary Table 5) and *Quality Assessment of Controlled Intervention Studies* (Supplementary Table 6). As shown in Supplementary Tables 5 and 6, the risk of bias in the reviewed literature was determined in both assessment tools using 14 distinct criteria (e.g., was the exposure(s) assessed more than once over time?) each of which was rated as "yes", "no", or "not applicable". For each criterion, each study was scored between 0 and 1, where "yes" indicated the presence of a risk and equalled a score of 1 and "no" indicated the absence of a risk and a score of 0. The risk of bias was assessed for each study across all criteria, and for each criterion across the literature, and across the literature for all criteria. To this end, we used the mean rating of each criterion, which was then classified as low risk (>0.2 out of 1), moderately low risk (0.3), moderate risk (0.4–0.5), or high risk (<0.5).

The fMRI-neurofeedback-specific methodological quality of the literature was assessed using the *Consensus on the Reporting and Experimental Design of Clinical and Cognitive-Behavioural FMRI-neurofeedback Studies* (CRED-NF; Ros et al., 2020). Each item was classified as "yes", "no", or "not applicable", where "yes" equalled a score of 1 and "no" a score of 0 (Supplementary Table 7). The methodological quality was assessed for each study across all criteria, and for criterion across the literature, and across the literature for all criteria using the mean of each criterion and was classified as high (>0.8 out of 1), moderately high (0.7), moderate (0.5–0.6) or low (<0.5). It should be noted that a high score in the CRED-NF checklist implies high methodological quality (i.e., desired) whereas a high score in the risk of bias tools implies a high risk of bias (i.e., undesired).

3. Results

3.1. Overview of the socio-demographic and substance use characteristics of the reviewed samples

Table 1 describes the characteristics of the 16 studies included for review. The literature to date examined 445 participants, of which 290 were male, 112 female, and 43 unreported. The reviewed samples were aged a mean of 34 years, with a range from 21-to-65 years. The average total sample size was 28 participants per study (including SUD and control groups), ranging from 4 to 52 participants.

The literature included three distinct SUDs, most commonly tobacco (56 %; 9/16 studies), followed by alcohol (38 %; 6/16), and cocaine (6 %; 1/16). The definition of SUDs varied between studies. Half of the studies (50 %; 8/16) investigated individuals with tobacco dependence who consumed a mean daily dosage of 16 cigarettes (range = 13-to-20) and an average duration of use of 14 years (range = 7-to-26). Single studies examined participants with alcohol use disorder (AUD) and cocaine dependence who consumed, on average 32 standard drinks and 0.3 g of cocaine per day, respectively (Kirschner et al., 2018; Subramanian et al., 2021). Please refer to supplementary information (Section 1 & 2) for further description of the reviewed sample.

3.2. Overview of fMRI-neurofeedback methods

3.2.1. Methods to analyse fMRI-neurofeedback data on brain function in real-time

The method to analyse the *fMRI-neurofeedback signal* in *real-time* varied between studies. Most studies (88 %; 14/16), derived the real-time fMRI-neurofeedback signal from the activity of one or more regions-of-interest (ROI). Two studies combined ROI-target activity and functional connectivity. In most studies (75 %; 12/16), ROI-targets were functionally localised during the training run (e.g., the top 33 % of activated voxels) while participants performed either a cue-induced

Table 2
Neurobehavioural changes *pre-to-post fMRI-neurofeedback*.

Author, year	Methods		Results		
	NF task	fMRI offline analysis	Craving	Brain functional changes	ROI-craving correlation
Sanader Vukadinovic, 2024	⇓	seed-based connectivity	_	↓ ventral attention network	_
Fede, 2023	⇓	ROI (ACC, dlPFC, insula, striatum, VTA/SN)	=	↓ ACC, dlPFC, insula	positive
Chung, 2023	⇑	ROI (striatum)	↑	↑striatum	_
Karch, 2022	⇓	whole brain	↓	↓ dACC, insula, MFG, central gyrus	_
Subramanian, 2021	⇓	ROI (rACC, insula, striatum)	↓	_	_
Kim, 2021	⇑	ROI (ACC, mPFC, OFC)	↓	↑ ACC, mPFC, OFC	negative
Rana, 2020	⇓	ROI (insula)	↓	↓ insula	_
Kirsch, 2016	⇓	ROI (striatum)	=	↓ striatum	=
Karch, 2015	⇓	ROI (ACC, dlPFC, insula)	↓	_	_
Kim, 2015	⇑	ROI I (ACC, mPFC, OFC)	=	↑ ACC, mPFC, OFC	negative
		ROI II (PCC, precuneus)		↑ PCC, precuneus (ROI+FC NF only)	=
		seed-based connectivity		↑ ACC, mPFC, OFC, PCC, precuneus (ROI+FC NF only)	negative
Canterberry, 2013	⇓	ROI (ACC)	↓	_	_
Hanlon, 2013	⇓	ROI (ACC)	↓	_	_
Li, 2013	⇓	ROI (ACC)	↓	↓ ACC	_

Acronyms: ACC, anterior cingulate cortex; dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; FC, functional connectivity; fMRI, functional magnetic resonance imaging; MFG, medial frontal gyrus; mPFC, medial prefrontal cortex; NF, fMRI-neurofeedback; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; PFC, prefrontal cortex; rACC, rostral anterior cingulate cortex; ROI, region of interest; SN, substantia nigra; VTA, ventral tegmental area; '=', no significant change; '_' not investigated/not applicable/ not provided; '⇑', increase target regions; '⇓', decrease target regions; '↓', decrease, '↑', increase.

Table 3
Neurobehavioural changes in fMRI-neurofeedback, *between fMRI-neurofeedback and control conditions.*

Author, year	Methods		Results				
	NF task	fMRI offline analysis	Conditions compared	Subject	Craving	Brain functional changes	ROI-craving correlation
Fede, 2023	⇓	ROI (ACC, dlPFC, insula, striatum, VTA/SN)	ROI vs iSVM	between	=	↓ ACC, insula, striatum	_
Chung, 2023	⇑	ROI (striatum) whole brain	NF vs no NF	between	=	↑ striatum ↑ insula, right inferior frontal	_ _
Karch, 2022	⇓	whole brain	NF vs control	between	=	↓ dACC, caudate, cuneus, precuneus, medial occipital	=
Subramanian, 2021	⇓ ⇑	ROI I (rACC, insula, striatum) ROI II (vlPFC)	NF vs control	between	=	↓ rACC, insula, striatum *trend* =	positive _
Karch, 2019	⇓	whole brain	relapse vs abstinent	between	_	↑ ACC, caudate, MFG	=
Kirschner, 2018	⇓	ROI (VTA/SN)	NF vs no NF	within	_	↑ VTA/substantia nigra	_
Kirsch, 2016	⇓	ROI (striatum) whole brain	NF vs control vs no NF	between	↓ _	↓ striatum ↑ right inferior frontal	_ _
Hartwell, 2016	⇓	ROI (PFC)	NF vs no NF	between	↓	↓ PFC	_
Karch, 2015	⇓	ROI (ACC, dlPFC, insula) whole brain	NF vs no NF	within	_ _	↓ ACC, insula, dlPFC ↓ ACC, insula, dlPFC, MFG, inferior temporal, cuneus	_ _
	Rest	seed-based connectivity			_	↑ DMN	_
Kim, 2015	⇑	ROI I (ACC, mPFC, OFC) ROI II (PCC, precuneus) seed-based connectivity	ROI+FC vs ROI	between	=	= ↑ PCC, precuneus ↑ ACC, mPFC, OFC, PCC, precuneus	_ _ _
Canterberry, 2013	⇓	ROI (ACC)	NF vs no NF	within	_	↓ ACC	=
Hanlon, 2013	⇓ ⇑	ROI (ACC) ROI (mPFC)	NF vs no NF	within	_ _	↓ vACC = PFC	_ _
Li, 2013	⇓ ⇓ ⇑	ROI (ACC) whole brain ROI (mPFC)	NF vs no NF	within	_ _ _	↓ ACC ↓ ACC, PFC, hippocampus, NAcc = mPFC	_ positive _

Acronyms: ACC, anterior cingulate cortex; dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; DMN, default mode network; FC, functional connectivity; fMRI, functional magnetic resonance imaging; iSVM, intermittent support vector machine; MFG, medial frontal gyrus; mPFC, medial prefrontal cortex; NAcc, nucleus accumbens; NF, fMRI-neurofeedback; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; PFC, prefrontal cortex; rACC, rostral anterior cingulate cortex; ROI, region of interest; SN, substantia nigra; vACC, ventral anterior cingulate cortex; vlPFC, ventrolateral prefrontal cortex; VTA, ventral tegmental area. '=', no significant change; '_' not investigated/not applicable/ not provided; '⇑', increase target regions; '⇓', decrease target regions; '↓', decrease, '↑', increase.

craving or specific cognitive task (e.g., monetary reward task). In 25 % (4/16) of studies, ROI-targets were anatomically defined. Please refer to supplementary information (Section 3 & 4; Supplementary Table 8) for a more detailed description of neurofeedback-related analysis.

As shown in Fig. 3A, the ACC was the most consistently used ROI-target (63 %; 10/16 studies), followed by the insula (44 %; 7/16), striatum (25 %; 4/16), dorsolateral prefrontal cortex (dlPFC, 31 %; 5/16), PFC (19 %; 3/16), ventral tegmental area (VTA) combined with substantia nigra (13 %; 2/16), and other frontal regions in individual studies (6 %; 1/16) e.g., medial orbitofrontal cortex (mOFC) and the superior frontal cortex.

3.3. Overview of parameters used for experimental designs

Fig. 4 overviews the key experimental and design parameters used in the literature (for a more detailed description, see Supplementary Table 8). Cue-induced craving was the most commonly used fMRI-neurofeedback *task* (88 %; 14/16 studies), where the aim was to regulate brain *function* and reduce *craving* while viewing substance-related visual cues (see Fig. 1). Two studies used non-cue-induced craving fMRI-neurofeedback, where the task was to modulate the *function* of reward-related brain regions while performing positive mental imagery tasks, without substance-related cues. With one exception (Fede et al., 2023), participants were given *general instructions* to either: i) down-regulate (e.g., 'decrease the thermometer' [56 %; 9/16]), ii) up-regulate (e.g., 'increase the thermometer' [25 %; 4/16]), or iii) up- and down-regulate (19 %; 3/16 studies) the activity of the neurofeedback target.

Control conditions varied across the reviewed literature. Roughly 43 % (7/16) of the studies included an *active placebo-controlled group* (e.g., mock feedback derived from a different time point or ROI-target). In contrast, 19 % (3/16) of studies compared various types of fMRI-neurofeedback, such as ROI-activity-based compared to ROI-functional connectivity-based. The remaining 38 % (6/16) of studies did not include an active control group and did not compare neurofeedback types.

3.4. fMRI-neurofeedback-related neurobehavioural changes

3.4.1. Neurobehavioural changes pre-to-post fMRI-neurofeeback

All the reviewed studies investigated the neurobehavioural changes *pre-to-post fMRI-neurofeedback*, measured as changes from the first-to-last fMRI-neurofeedback run (14 studies) or from the pre-training run to the transfer run (2 studies; see Table 2 overview).

3.4.1.1. Brain function. As shown in Fig. 3B, there was mixed evidence that brain activity changed *pre-to-post fMRI-neurofeedback* (57 %; 8/14). Changes were located most consistently in the ACC (29 %; 4/14), followed by the insula (21 %; 3/14), PFC and striatum (14 %; 2/14 studies). Two studies (13 %; 2/16) assessed *pre-to-post* changes in functional connectivity, and they reported significant changes in the ventral attention network and prefrontal regions (e.g., ACC, mOFC, PFC).

3.4.1.2. Craving and mental health. All but two studies investigated changes in *craving pre-to-post fMRI-neurofeedback*, with over half showing a significant craving reduction (57 %; 8/14, Table 2). There was emerging evidence of reduced substance use and *mental health symptom scores* (e.g., reduced depressive symptomology) *pre-to-post fMRI-neurofeedback*, but this was only examined by 2 (13 %) and 3 (19 %) studies, respectively.

Table 4
Overview of between-subject effects of *intervention-by-time* on brain and behavior.

Author, year	Methods		Results		
	NF task	fMRI offline analysis	Conditions compared	Craving	Brain functional changes
Chung, 2023	⇑	ROI	NF vs control	=	↑ striatum, *trend*
		whole brain		_	↑ right inferior frontal
Karch, 2022	⇓	whole brain	NF vs control	=	=
Subramanian, 2021	⇓	ROI I (rACC, insula, striatum)	NF vs treatment as usual	=	=
Kim, 2021	⇑	ROI I (ACC, mPFC, OFC)	ROI + FC vs ROI	↓	_
Kirsch, 2016	⇓	ROI	NF vs control vs no NF	↓	_
		whole brain			_
Hartwell, 2016	⇓	ROI	NF vs control	=	= PFC
Karch, 2015	⇓	ROI	NF vs control	_	= ACC, dlPFC, insula

Acronyms: ACC, anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; FC, functional connectivity; fMRI, functional magnetic resonance imaging; mPFC, medial prefrontal cortex; NF, fMRI-neurofeedback; OFC, orbitofrontal cortex; PFC, prefrontal cortex; rACC, rostral anterior cingulate cortex; ROI, region of interest; '=', no significant change; '_' not investigated/not applicable/not provided; '⇑', increase target regions; '⇓', decrease target regions; '↓', decrease, '↑', increase.

3.4.1.3. Brain-behaviour correlations. There was emerging evidence for significant correlations between functional changes *pre-to-post fMRI-neurofeedback* and: craving reduction *pre-to-post fMRI-neurofeedback* (70 %; 4/6), baseline severity of dependence (66 %; 2/3), and substance use at follow-up [100 %; 2/2 studies] (Table 2).

3.4.2. Neurobehavioural differences between fMRI-neurofeedback and control conditions

As overviewed in Table 3, all studies investigated neurobehavioural differences between distinct *control conditions*, defined as *within-subject* (e.g., no fMRI-neurofeedback vs fMRI-neurofeedback) and *between-subject* (e.g., mock fMRI-neurofeedback from a different time point compared to fMRI-neurofeedback). The compared conditions include fMRI-neurofeedback compared to an active or passive control condition, one type of fMRI-neurofeedback compared to another, or individuals who remained abstinent compared to those who relapsed.

3.4.2.1. Brain functional differences: fMRI-neurofeedback vs control. As shown in Fig. 3C, there is consistent evidence of brain activity differences between fMRI-neurofeedback and *control conditions* (86 %; 12/14). The differences were localised most consistently in the ACC (43 %; 6/14), followed by the inferior frontal gyrus, striatum, and cuneus (21 %; 3/14).

More than half of these significant differences (57 %; 8/14 studies) relate to *between-subject* differences in brain activity between fMRI-neurofeedback and: an active placebo control (21 %; 3/14), no fMRI-neurofeedback (14 %; 2/14), and various types of fMRI-neurofeedback (14 %; 2/14). Additionally, two studies (13 %; 2/16) compared and reported differences in the functional connectivity of default mode/PFC regions between fMRI-neurofeedback and control conditions (Table 3).

Almost half of the significant reported differences (43 %; 6/14 studies) relate to *within-subject* effects where brain *activity* during fMRI-neurofeedback was compared to a baseline no-fMRI-neurofeedback condition (e.g., passive control).

3.4.2.2. Craving differences: fMRI-neurofeedback vs control. There was emerging evidence of *control condition* differences in craving with 29 % (2/7) of studies that investigated this finding significantly lower craving after fMRI-neurofeedback compared to a no-fMRI-neurofeedback group (Table 3).

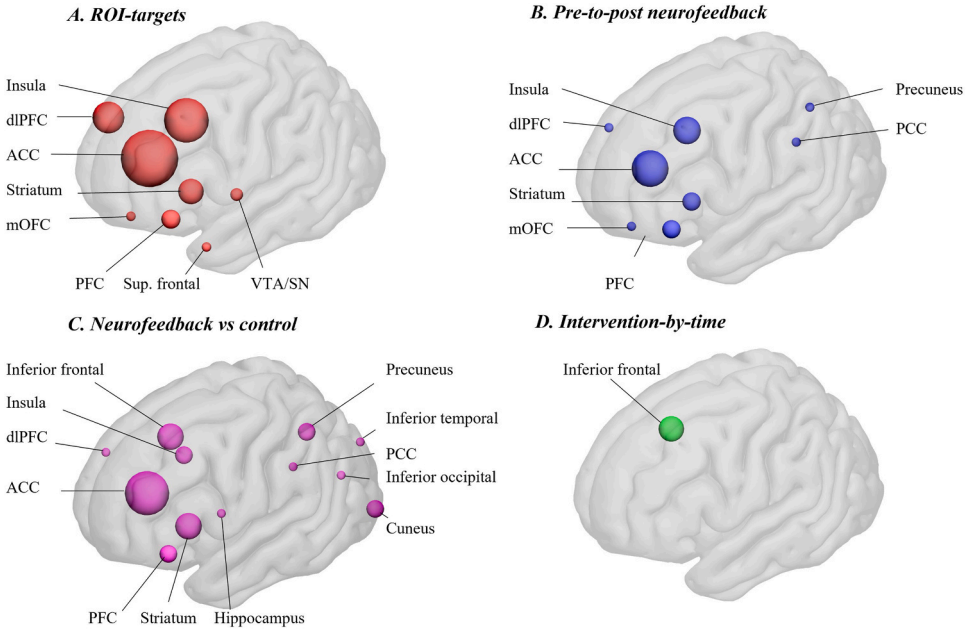


Fig. 3. Overview of ROI targets and fMRI correlates of fMRI-neurofeedback, mapped onto the brain surface. The mapping was performed with Surf Ice (https://www.nitrc.org/projects/surfice/) using MNI brain coordinates derived from the meta-analytic tool Neurosynth (https://neurosynth.org/analyses/terms/). The node size was calculated based on the number of studies finding significant effects in that region (e.g., larger nodes are those where significant effects were more frequently found). Acronyms: ACC, anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; mOFC, medial orbitofrontal cortex; PCC, posterior cingulate cortex; PFC, prefrontal cortex; ROI, region of interest; Sup. frontal; superior frontal cortex; VTA/SN, ventral tegmental area/substantia nigra.

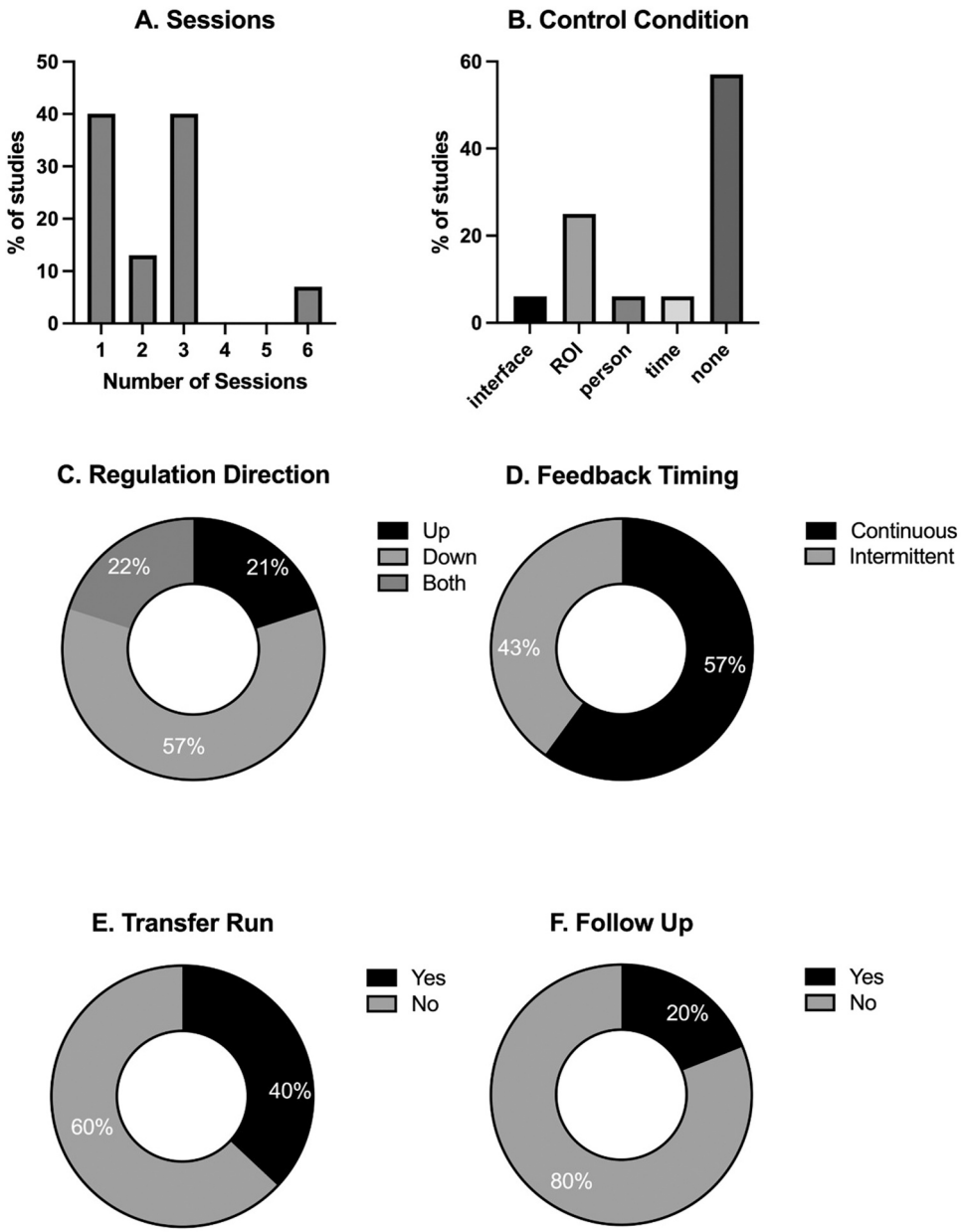


Fig. 4. Overview of key features of the fMRI-neurofeedback study design in the reviewed studies. A) The percentage of studies that include specific numbers of fMRI-neurofeedback sessions (e.g., 6 % of studies included 6 fMRI-neurofeedback sessions). B) The percentage of studies that included specific control types (e.g., 6 % of studies used the activity from a different person). C) The percentage of studies that included different desired regulation directions (e.g., 27 % of studies aimed to upregulate target activity). D-F) The percentage of studies that included continuous or intermittent feedback (D), a transfer run (E), and a behavioural follow-up (F).

3.4.2.3. Brain-behaviour correlations. Five studies investigated correlations between brain functional differences and craving. Of these, two (2/5; 40 %) studies reported significant brain function-craving correlations (Table 3).

3.4.3. Intervention-by-time neurobehavioural changes

3.4.3.1. Brain functional changes. As per Table 4, less than half of the studies investigated *intervention-by-time* effects on *brain activity* (41 %; 7/16), with one study (1/7; 14 %) reporting increased activity in the inferior frontal gyrus in fMRI-neurofeedback vs mock fMRI-neurofeedback (Chung et al., 2023).

3.4.3.2. Craving changes & brain-behaviour correlations. There is inconsistent evidence of *intervention-by-time* effects on craving with two out of six studies (33 %) demonstrating a significant reduction in craving *pre-to-post* fMRI-neurofeedback between distinct fMRI-neurofeedback control conditions. None of the six studies found a significant *association* between *intervention-by-time* changes in brain activity and behaviour. Similarly, no study examined significant *intervention-by-time* effects on *substance use* or other *behavioural measures*.

3.5. Assessment of the methodological quality of the literature

The literature had a moderately low risk of bias for the NIH tool for cross-sectional studies comparing *fMRI-neurofeedback and control conditions*, with a within-average study score of 0.25 (range = 0–0.93; see Supplementary Table 5, National Institutes of Health, 2014a). Further, the controlled intervention studies had a moderate longitudinal risk of bias, with an average within-study score of 0.44 (range = 0–0.93; see Supplementary Table 6, National Institutes of Health, 2014b). The

methodological quality of the fMRI-neurofeedback studies was moderate as per CRED-NF checklist, with an average within-study score of 0.60 (range = 0.53–0.75; see Supplementary Table 7; Ros et al., 2020)

4. Discussion

To our knowledge, this is the first systematic review of the neurobehavioral effects of fMRI-neurofeedback studies in SUDs. There was emerging evidence that the function of key brain regions posited to underpin SUDs is changed by fMRI-neurofeedback, most consistently the ACC (implicated in craving and decision making), the PFC (implicated in disinhibition), and the insula [implicated in interoception] (Koob and Volkow, 2016). The consistency of the findings varied as a function of the design examined, with consistent *between-condition*, inconsistent *over-time,* and largely non-significant *intervention-by-time* effects on the brain and craving. Overall, the evidence had a low-to-moderate risk of bias.

The direction of brain changes was mixed across the literature and might have reflected participants' approach to craving regulation (e.g., increased activity when the task was to increase the parameter shown in the BCI, such as increased temperature in the thermometer). However, most consistently, the reviewed evidence from *cross-sectional* and *repeated-measure* designs suggests that fMRI-neurofeedback can down-regulate the function of prefrontal-insular brain regions posited to underlie altered cognition in SUD: decision-making [ACC], inhibition [PFC], and interoception [insula]; Koob and Volkow, 2016). Of note, prefrontal-insular regions are hyperactive during cue-induced craving in SUDs (Noori et al., 2016; Sehl et al., 2021). Therefore, the fMRI-neurofeedback-mediated change in activity of prefrontal-insular regions may represent the dampening of the incentive-salience network via the cortical (i.e., top-down) inhibition of striatal activity in SUDs (Koob and Volkow, 2016). However, the fact that striatal changes were less consistently observed suggests that this fMRI-neurofeedback-mediated cortical inhibition might have been insufficient to lead to downstream effects to reduce striatal functional alterations.

Overall, the reviewed evidence from cross-sectional studies (i.e., fMRI-neurofeedback vs control) and pre-to-post neurofeedback, points to the feasibility of fMRI-neurofeedback to reduce cue-induced craving in SUDs. Subjective craving is a central feature of SUDs (American Psychiatric Association, 2013; Skinner and Aubin, 2010). Indeed, cue-induced craving is associated with a hyperactive neural response (Noori et al., 2016; Sehl et al., 2021), increased self-reported craving (Schacht et al., 2013; Sehl et al., 2021), SUD severity (Jasinska et al., 2014), and the likelihood of future substance use/relapse (Courtney et al., 2016; Moeller and Paulus, 2018). As a consequence, cue-induced subjective craving and the associated neural hyperactivity are important targets for SUD treatment (Alizadehgoradel et al., 2020; Childress et al., 1993; Gay et al., 2022; Haass-Koffler et al., 2014). Therefore, given that fMRI-neurofeedback can change core neural circuitry and craving in SUD, fMRI-neurofeedback could be a feasible non-invasive intervention for SUD. However, the efficacy (and specificity) of fMRI-neurofeedback to induce the above-mentioned neurobehavioural changes in SUDs needs to be confirmed with *placebo-controlled* and *intervention-by-time* designs, which are lacking in the current literature (see CRED-NF in Supplementary Table 7).

There is emerging evidence that changes in ACC, PFC, and insula activity correlated with reduced subjective craving. Thus, changes in prefrontal-striatal activity may have underpinned subjective craving reduction. However, the evidence was mixed and partially supports this point. Alternatively, the findings on brain functional changes during fMRI-neurofeedback may reflect an implicit cue-induced craving response (Noori et al., 2016). Indeed, a threshold of brain activity may be required to induce changes in subjective craving (e.g., ACC activity may have to change by a certain percentage so that changes in subjective craving can be detected). The inconsistent brain-behaviour correlations might either reflect that the association between fMRI-neurofeedback-related brain changes and craving is moderated by some variables (e.g., SUD severity or personality factors [see Marxen et al., 2016]; or methodological limitations in measuring outcome variables). These include but are not limited to the lack of assessment of brain-behaviour correlations (n = 9 studies; see Supplementary Table 7) and the over-reliance on subjective craving measures. To fully elucidate the relationship between fMRI-neurofeedback-related brain changes and craving, future studies should i) systematically investigate the correlation between brain and craving changes, ii) include growth models that allow for random intercepts and slopes, and iii) examine the effect of fMRI-neurofeedback on psychophysiological responses measuring craving that could occur without participants' awareness (e.g., heart rate variability; Carter and Tiffany, 1999).

There was emerging evidence that participants with SUDs could use the psychological strategies learned during fMRI-neurofeedback to successfully modulate craving during transfer runs (Kim et al., 2021, 2015); and of reduced substance use following fMRI-neurofeedback (Rana et al., 2020; Subramanian et al., 2021). Thus, participants may have been able to implement the fMRI-neurofeedback learned strategies to manage craving to reduce their substance use, following the intervention. This is consistent with non-SUD studies, where fMRI-neurofeedback-related effects have been demonstrated to persist over prolonged periods (e.g., up to 14 months after the first neurofeedback scan; Rance et al., 2018; Robineau et al., 2017). In order for fMRI-neurofeedback to become a viable treatment option for SUDs, a key next step is to examine how personalised strategies learned during fMRI-neurofeedback are effective in real-life contexts and their link to craving and substance use (Ekhtiari et al., 2016). To this end, future longitudinal work is warranted to examine the transferability of the fMRI-neurofeedback-learned craving modulation techniques to transfer runs inside the MRI scanner, different contexts outside the MRI scanner, and how these effects last over time (via behavioural follow-ups).

4.1. Limitations of the literature to date

The findings of the literature to date need to be considered with caution considering methodological limitations. First, over 70 % of the literature did not include an active placebo control condition (see CRED-NF Supplementary Table 7). Thus, the observed neurobehavioural effects may be due to factors independent of fMRI-neurofeedback, such as placebo/expectation effects, arousal, and psychological strategies used to regulate brain function (Sorger et al., 2019). While more methodological investigation is required to elucidate the most effective form of mock fMRI-neurofeedback (Sorger et al., 2019), we recommend that future studies include active control conditions e.g., ROI-activity from a different time point/neurofeedback run. Second, the literature inconsistently adhered to the current consensus on the reporting and experimental design for neurofeedback studies (i.e., CRED-NF; Ros et al., 2020). For example, most studies demonstrated robust reporting consistency in the methodological items relating to feedback specification (e.g., hardware and software specification, online feature extraction). However, the literature demonstrated low reporting consistency in the pre-and post-experiment methodological items, such as preregistering the planned protocol and analyses and uploading raw data to an open-access data repository. Consistent adherence to the CRED-NF is required so that informed decisions can be made regarding the methodological effectiveness of reviewed studies. Third, as shown by the risk

of bias assessment (Supplementary Table 5), the literature included small sample sizes (Average number of participants exposed to real neurofeedback = 15, range = 4-to-26), and, thus, may be underpowered to reliably detect small-to-medium effects of fMRI-neurofeedback on brain function [$d < 0.2$-to-0.5] (Tursic et al., 2020). Larger samples are needed to confirm with precision the neural changes associated with fMRI-neurofeedback. Fourth, a substantial portion of the literature (i.e., ~ 50 %) of studies administered a single fMRI-neurofeedback session. However, at least two sessions of fMRI-neurofeedback might be required to observe lasting neural and behavioural effects (Fede et al., 2020), and confirmation studies with multiple assessment times are required to confirm the clinical significance of the findings. Fifth, to date, fMRI-neurofeedback has been exclusively investigated in samples with nicotine or alcohol dependence. Future research should investigate the use of fMRI-neurofeedback in highly prevalent and debilitating SUDs (e.g., opioid/stimulant/cannabis use disorders) and behavioural addictions that share common neural mechanisms with SUDs, such as food addiction and gambling (Balodis and Potenza, 2020; Lindgren et al., 2018). Finally, the reviewed literature findings relied on ROI methods to analyse brain data post-fMRI-neurofeedback. While hypothesis-driven, the ROI method can increase the likelihood of false positives, and preclude detecting regions other than ROIs that could be relevant for SUDs and fMRI-neurofeedback (Gentili et al., 2019). Future research should employ a combination of ROI and whole-brain approaches to balance theory-driven frameworks with the discovery of novel treatment targets.

4.2. Limitations of this review

The present review is characterised by several limitations. First, a meta-analytic approach was not feasible due to the heterogeneous design of the reviewed studies (e.g., within compared to between subjects, cue-induced rather than non-cue-induced neurofeedback, different ROI-targets). Second, we excluded grey literature (e.g., pre-prints, dissertations, conferences) meaning that publication biases might have led to the current literature review over-representing significant findings (Dwan et al., 2013). Third, the exclusion of non-English studies may have limited this systematic review since any evidence published in a non-English language would have been missed. However, recent evidence suggests that the exclusive reliance on English might have no impact on systematic review findings and quality (Dobrescu et al., 2021).

5. Conclusion

Overall, there is consistent cross-sectional evidence of brain functional and, less consistently, craving changes in fMRI-neurofeedback compared to passive or active control *conditions* in several regions implicated in prominent neuroscientific theories of addiction (e.g., ACC, PFC, insula). There is less consistent evidence that brain function and craving changed *pre-to-post* fMRI-neurofeedback, in prefrontal-striatal and insular regions and emerging findings of correlations between *pre-to-post* brain functional changes and reduced craving. Finally, the evidence of *intervention-by-time* effects on craving and brain function was lacking. The specificity of these neurobehavioural effects is limited by the lack of placebo-controlled and *intervention-by-time* results as well as various methodological limitations, demonstrated by a low-to-moderate risk of bias and moderate methodological quality of the literature. Future research adopting robust experimental designs with an active placebo control, follow-up assessments, and transfer runs across a wide array of SUDs are warranted to confirm how fMRI-neurofeedback can change brain alterations and craving in SUDs, and how these changes relate to relapse and changes in substance use-related problems over time.

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No generative AI or AI-assisted technologies were used during the preparation of this work.

Declaration of Competing Interest

The authors have no competing interests to declare. GP was employed by Braincast Neurotechnologies.

Data Availability

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2024.105865.

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