



Differences in fMRI-based connectivity during abstinence or interventions between heroin-dependent individuals and healthy controls

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ARTICLE INFO

Keywords:

Heroin dependence
Functional connectivity
Addiction
Opioid
fMRI

ABSTRACT

The substantial personal, societal, and economic impacts of opioid addiction drive research investigating how opioid addiction affects the brain, and whether therapies attenuate addiction-related metrics of brain function. Evaluating the connectivity between brain regions is a useful approach to characterise the effects of opioid addiction on the brain. This work is a systematic narrative review of studies investigating the effect of abstinence or interventions on connectivity in people who are dependent on heroin (HD) and healthy controls (HC). We found that HD typically showed weaker connectivity than HC between three functional networks: the Executive Control Network, Default Mode Network, and the Salience Network. Abstinence and Transcranial Magnetic Stimulation (TMS) both attenuated differences in connectivity between HD and HC, often by strengthening connectivity in HD. We observed that increased connectivity due to abstinence or TMS consistently related to decreased craving/risk of relapse. Using these findings, we present an “urge and action framework” relating therapeutic factors contributing to craving/relapse, connectivity results, and neurobiological models of HD. To inform future research, we critically assessed the impact of study design and analysis methods on study results. We conclude that the weaker between-network connectivity in HD and HC and its relationship to craving/relapse merits further exploration as a biomarker and target for therapeutic interventions.

1. Introduction

Illicit drugs were estimated to cost the UK £ 20 billion in 2020 (Black, 2021) and \$1.02 trillion in the US in 2017 (Florence et al., 2021). The current cost of addiction and problematic drug use (r), is likely growing, given that substance use disorders (SUD) showed the first and second-highest increase in percent change of disease burden between 1990 and 2019 for women and men, respectively (McKee et al., 2021). Out of all drugs of problematic use, opioids were the largest contributor to the record high in illicit drug-related mortality in 2018 in the UK (Black, 2021). In the US, nearly 135 people died per day in 2019 from opioid-related deaths (Center for Disease Control and Prevention, 2022). The substantial health, social, and economic impacts of problematic opioid use and the growing number of those developing dependence necessitates research of the associated neural correlates, and whether they are attenuated by therapeutic interventions.

As with all addictions (ICD-10/11) or (DSM-IV dependence, DSM-5

severe opioid use disorder) opioid dependence is characterised by chronic cycles of relapse and remittance, which relate to dysfunctional neural circuitry underpinning impulse control, decision-making, emotional regulation, stress response, and reward processing (Hayes et al., 2020; Koob, 2009; Kozak et al., 2019; Kwako et al., 2016; Moeller and Paulus, 2018; Uhl et al., 2019; Wilcox et al., 2019). Effective therapies that result in maintained abstinence have been shown to restore or attenuate these altered neural circuits (Koob, 2006; Koob and Volkow, 2010; Lueptow et al., 2020). Thus, characterising how the neural correlates of opioid dependence are affected by abstinence or therapeutic interventions will improve the development of therapeutic interventions.

1.1. Identifying the neural correlates of opioid addiction with neuroimaging

One way to characterise the neural correlates of opioid dependence

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<https://doi.org/10.1016/j.neubiorev.2025.106116>

Received 30 December 2024; Received in revised form 6 March 2025; Accepted 16 March 2025

Available online 22 March 2025

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is through functional magnetic resonance imaging (fMRI), by utilising the Blood Oxygenation Level Dependent (BOLD) signal as a proxy measure of neuronal activity (Detre and Wang, 2002). fMRI acquired during resting state captures spontaneous, intrinsic brain activity, whereas task-fMRI is used to probe the neural correlates of specific processes. For example, cue-reactivity tasks often show blocks of drug-related images, followed by blocks of neutral visual stimuli. People with opioid dependence tend to show higher BOLD activity in reward regions as compared with healthy controls (HC) in response to drug-related stimuli (Hayes et al., 2020).

Another way to use fMRI to assess the neural correlates of opioid dependence is to use connectivity measures, which typically evaluate the relationship between two or more brain regions. One common example is Functional Connectivity (FC), which measures the temporal correlation between spatially separated brain regions (Biswal et al., 1995; Fingelkurts et al., 2005). There are many ways to compute FC and other connectivity methods, each with trade-offs and considerations. In Box 1 we consider how the method by which researchers define brain regions impacts connectivity analysis. In Box 2 we provide an overview of common connectivity methods.

Box 1

Defining brain regions.

The first step of most connectivity analyses is to identify the regions from which timeseries of BOLD activity are extracted and compared. Dividing the cortex into discrete regions is known as parcellation, which can be broadly split into anatomical or functional approaches. Anatomical parcellation uses atlases that define brain regions based on morphological, structural, or cytoarchitectural characteristics (Amunts and Zilles, 2015). Functional parcellation defines brain regions by processes in which it is typically associated (Eickhoff et al., 2018). For example, one of the earliest fMRI studies presented participants with a checkerboard visual stimulus, and in response, the posterior occipital cortex exhibited an increased magnitude of the BOLD signal, associating its function with vision (Kwong et al., 1992). It is best practice to use functional parcellation (especially for cortical regions) for connectivity analyses, as regions defined anatomically may have functional variation and thus obscure the ability to assess the role of the region in the function under evaluation (Bijsterbosch et al., 2019). Within functional atlases, brain regions can be defined either by discrete boundaries, referred to as hard parcellations, or with non-distinct boundaries, known as soft parcellations.

One consideration for atlas-based parcellations is whether to parcellate data in standard vs subject space. The former is more common, as registering subject's functional data to standard space is often included in preprocessing, and subsequent parcellation using an atlas in standard space is straightforward. However, distortions are inevitable when registering subject data to standard space, resulting in heterogeneous changes in regional volume, and potential misalignment of spatial boundaries (Allen et al., 2008). This negatively impacts connectivity analysis, since average regional timeseries will be influenced by voxels inappropriately grouped within a region (Bijsterbosch et al., 2019; Smith et al., 2011). By conducting analyses in subject space, researchers can be more confident their results are not driven by artefacts associated with spatial registration.

A more advanced method of subject-level parcellation is to conduct individual functional parcellation. This approach uses participant's neuroimaging data to inform personalised boundaries between regions (Kong et al., 2019; Laumann et al., 2015; Wang et al., 2015).

Atlas-based parcellations are not the only way to define regions from which connectivity is quantified; studies may also define regions based on their engagement during conditions of interest (e.g., blocks of drug-related stimuli in a cue reactivity task). For example, a study may identify a region related to dysfunctional reward processing in people with opioid addiction based on a meta-analysis's identification of voxels that show reliable group differences during a cue reactivity task. Another approach is to employ Independent Component Analysis (ICA), which identifies voxels or regions that are reliably engaged in a particular condition (Duff et al., 2012).

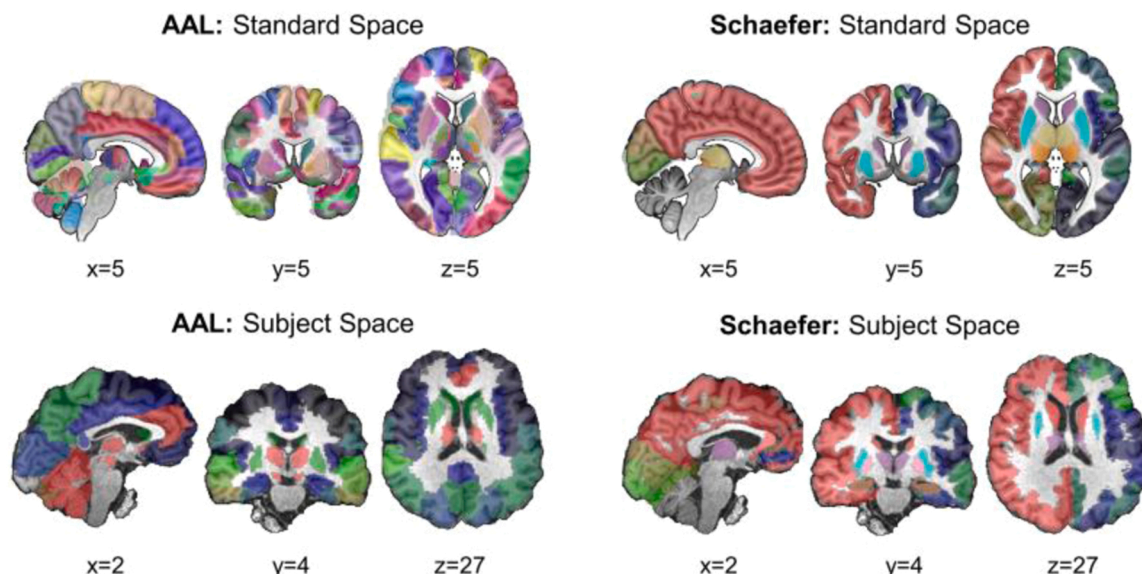


Fig. 1. Example of (A) anatomical and (B) functional atlases. (A) The Automated Anatomical Labelling (AAL) atlas is overlaid on (Ai) a standard MNI brain and (Aii) after transformation to subject space. The Schaefer atlas in (Bi) standard MNI space and (Bii) subject space is an example of a functionally derived parcellation (Schaefer et al., 2018). In all panels, colours demarcate different brain regions. Sagittal, coronal, and transverse slices are provided by the x, y, and z coordinates, respectively.

Box 2

How is functional connectivity defined?

There is a large variety of methods to compute connectivity, which can be broadly characterised using two axes - directed vs undirected, and model-based vs model-free (Farahani et al., 2019; Li et al., 2009; Rogers et al., 2007). Both directed and undirected connectivity approaches assess whether two timeseries are related; however, directed measures also capture whether the relationship is driven by one region's influence over another. Directed measures of FC, referred to as Effective Connectivity (EC), are better suited for establishing hierarchies of interregional control because they evaluate the influence of one region over another, instead of a general relationship between the two. Like FC, there are a variety of approaches researchers can employ to evaluate EC. Granger Causality (GC) (Goebel et al., 2003) and Dynamic Causal Modelling (DCM) (Friston et al., 2003) are two popular model-based approaches.

A common example of an undirected FC approach is correlation between two timeseries, where a correlation coefficient indicates the strength of interregional relationships, but not whether one region is influencing another.

Model-based methods are the more common form of FC analysis. They work by extracting the timeseries of BOLD activity from a brain region and computing the relationship between other regional timeseries. A common model-based FC approach is to compute the correlation or coherence between pairs of timeseries (Biswal et al., 1995; Greicius et al., 2003; Wig et al., 2011). Psychophysiological interactions (PPI) are another model-based approach that works by modelling the influence of task conditions on pairwise connectivity (Cisler et al., 2014; Friston et al., 1997; O'Reilly et al., 2012).

Model-free FC approaches are data-driven, and do not consider regional specificity or task conditions - instead, model-based methods typically cluster or reduce the dimensionality of the data. Clustering-based FC is less common than dimensionality reduction approaches, and for more information, see the following references (Cordes et al., 2002; Golay et al., 1998; Seghier, 2018). Dimensionality reduction approaches include principal component analysis (PCA) and independent component analysis (ICA), which identify components of spatial or temporal connectivity (Calhoun et al., 2009).

While this section provides a snapshot of the breadth of FC approaches, there is little consensus as to which approaches are superior. Direct evaluation of both model-based vs model-free (Baumgartner et al., 1998; Worsley et al., 2005) and directed vs undirected (Conti et al., 2019) approaches showed comparable performance. Since each connectivity method has trade-offs and limitations, it is sensible to choose an approach based on the aims of each study (Li et al., 2009). For example, model-based methods facilitate targeted exploration of how regions interact with other regions, whereas a model-free approach is unconstrained by assumptions underpinning parcellation; undirected FC methods can tractably characterise how all pairs of regions coordinate during a condition, whereas directed connectivity methods are more useful in establishing a hierarchy of function among a group of regions (Ray et al., 2021; Rolls et al., 2022; Vaudano et al., 2009).

Connectivity analysis is especially useful for understanding how brain regions work together to subserve complex, distributed processes impaired in opioid dependence. Here we first describe the role of functional networks; then, we introduce their relationship to studies investigating differences between people with opioid dependence and HC.

1.2. The role of functional networks

Groups of regions that reliably coactivate or connect in a particular condition are deemed networks. For example, there are networks associated with different sensorimotor processes, such as the visual, somatosensory, auditory, and motor networks. Other notable networks support attention (e.g., dorsal attention network and Salience Network (SN)), reward processing (e.g., limbic and ventromedial networks), cognition (e.g., executive control network (ECN)), and resting state (Default Mode Network (DMN)) (Schaefer et al., 2018; Yeo et al., 2011). Investigating network topology (i.e., how/what regions are included in a network) and dynamics (i.e., prevalence and coordination among networks across time) informs how different groups utilise process-specific neural resources.

1.3. The relationship between network connectivity, clinically relevant metrics, and therapeutic targets

People with problematic drug use exhibit altered connectivity between networks involved with stress/emotion regulation and cognition as compared with HC (Belin et al., 2013; Dugré et al., 2023; Dunlop et al., 2017; Everitt and Robbins, 2016; Fareed et al., 2017). Illicit opioid dependence has been shown to affect connectivity in reward processing networks, the ECN, DMN, and SN (Chen et al., 2022; Jin et al., 2022; Li et al., 2018). Differences in connectivity across many functional networks indicate that the symptoms of illicit opioid dependence are not

limited to a single process, and may be attributed to the collective difficulties coordinating the many processes executed by multiple networks. Yet, it is unclear how therapeutic strategies may alter these putative neural correlates of illicit opioid dependence, and whether changes in connectivity relate to improvement in clinically relevant metrics.

1.4. Aims and objectives

The first aim of this systematic narrative review is to characterise the different effects of abstinence or interventions on connectivity between HC and people with illicit opioid dependence.

The studies we reviewed had to meet criteria for opioid dependence in DSM-IV or ICD 10/11, or severe opioid use disorder in DSM-5, with reference to their use of illicit opioids, i.e., heroin or opium. Our second aim is to evaluate whether the effects of abstinence or an intervention on connectivity is associated with clinical/behavioural outcomes. While there are recent reviews on differences in connectivity between HC and people with problematic drug use (Koob, 2021; Wilcox et al., 2019), our work focuses on illicit opioid dependence (e.g., heroin) rather than the effects of prescription opioids on connectivity reviewed by others (Mill et al., 2021; Upadhyay et al., 2010). Additionally, reviews on the neural correlates of opioid dependence tend to include both microscale (e.g., receptor-level changes) and macroscale measures (e.g., connectivity) of brain function, or focus on intrinsic differences between people with opioid dependence and HC (Herlinger and Lingford-Hughes, 2022; Moninka et al., 2019). Our focus on changes in connectivity in people with opioid dependence as a result of abstinence or an intervention increases the translational relevance of this review in three ways. First, developing an understanding of differences in connectivity can inform the delivery of targeted neuromodulatory, therapeutic interventions, such as noninvasive brain stimulation. Second, identifying an association between abstinence- or intervention-related changes in clinically

relevant effects (e.g., decreased craving or risk of relapse) and connectivity provides potential biomarkers and outcome measures for developing therapeutic/neuromodulatory interventions. Finally, our evaluation the impact of study methods on the reliability and generalisability of results enables improved approaches of future research.

2. Methods

This study was preregistered on PROSPERO (CRD42023418691). A literature search was carried out in April 2023 across the following 6 electronic bibliographic databases: MEDLINE, EMBASE, American Psychological Association (APA) PsycINFO, PsycArticlesFullText, Scopus and PubMed.

After removal of duplicates across databases, 438 papers remained. After removing articles classified as non-English language articles, narrative reviews, systematic reviews, conference abstracts/papers, dissertations, or qualitative studies (e.g., case studies, opinion pieces, letters, comments, editorials), 266 articles remained. These articles' title, abstract, and text were screened more closely to ascertain whether they met inclusion criteria by 3 reviewers, with 2 independent reviewers reviewing each article against the pre-defined inclusion and exclusion criteria (Table 1). This concluded in initially including 13 articles, with 33 articles that reviewers disagreed on. Disagreements about screening were resolved by discussion between all the 3 reviewers, which resulted in 9 out of the 33 articles moving to full text screening.

Full text screening was performed on the 22 articles agreed upon by all 3 reviewers. Each article was reviewed by two independent reviewers using a standardised data extraction document on Microsoft Excel with predefined columns following the PRISMA protocol guidelines (Page et al., 2021). The results of data extraction were checked for consensus across the two reviewers for each article and disagreements were settled through discussion. Out of the 22 articles that underwent full text screening, 6 were determined to not meet inclusion criteria. For example, two studies included rsfMRI in people with opioid addiction

and HC, but could not directly assess the effect of a task-based intervention on FC because tasks were performed outside the scanner (Li et al., 2013; Ma et al., 2015). It is notable that no studies that met the inclusion criteria investigated the effect of opioid substitution therapy (OST) on FC.

Thus, 16 articles were selected as the final dataset for qualitative, narrative synthesis of results in line with Synthesis Without Meta-analysis (SWiM) guidelines (Campbell et al., 2020) (Fig. 1). All studies included individuals who were dependent on heroin; thus, groups with opioid dependence will be referred to as heroin-dependent (HD) throughout this work.

When describing differences in connectivity between HD and HC, the term "stronger" or "higher" refers to the strength of the connectivity value. For example, if a study used a Spearman's correlation between two regional timeseries as a measure of connectivity and found Spearman's ρ was greater in HC vs HD, this would be described as stronger connectivity in HC vs HD.

3. Results

3.1. Demographics and population characteristics

The majority of studies reviewed in this work were conducted in China (Studies 1–13, Table 2), with the remaining 3 conducted in Switzerland (Studies 14–16). The average participant age in each study ranged from 32 to 49 years old. Eight studies included only male participants, and all 16 studies reported no significant difference in biological sex between HD and HC groups. Study designs included 7 comparative cohort studies between HC and HD, 2 randomised controlled trials, 1 non-randomised interventional trials and 6 cross-sectional studies. Opioid use disorder or dependence was classified primarily by DSM-IV or DSM-5 criteria. One study used ICD-10 criteria to define opioid addiction, and another used a prescription of Methadone-Maintained Therapy (MMT) (Study 16). Definitions of abstinence varied across studies and a wide range of defined abstinence length was represented. Eleven of 16 studies included individuals receiving OST, primarily methadone.

Most studies investigated the effects of abstinence on FC (Studies 1–11, Table 2). The remaining 5 studies utilised two other interventions; Transcranial Magnetic Stimulation (TMS, a form of noninvasive brain stimulation (studies 12–13) and acute administration of heroin (Studies 14–16).

3.2. Comparisons between HC and HD population changes in connectivity as a result of cue-reactivity tasks

All studies that investigated the effects of a cue-reactivity task were conducted in China (Studies 1–2, Table 2). Of the two cue-reactivity studies, one (Wei et al., 2021) (Study 1), showed that drug-related cues recruited stronger FC between two DMN regions, the Posterior Cingulate Cortex (PCC) - medial Prefrontal Cortex (mPFC), in HD with protracted abstinence (i.e., non-OST-maintained abstinence for 6 months) as compared with people with OST-maintained abstinence (Wei et al., 2021). Given there were no significant differences in FC between HD to HC, it is unclear whether OST- or non-OST-maintained abstinence restored FC in the direction of HC, and whether that related to decreased craving.

The other study collected data during both resting state and while participants performed a cue-reactivity paradigm (Liu et al., 2011) (Study 2, Table 2). During resting state, the authors reported that the medial frontal gyrus had greater degree (i.e., number of connections to other regions) in HD as compared with HC. Conversely, the Anterior Cingulate Cortex (ACC) had a lower degree in HD as compared with HC. Relationships between rsfMRI degree and activity during the cue reactivity task were observed. The weakened FC in HD from the medial frontal gyrus was negatively correlated with both heroin cue-related

Table 1
Study inclusion and exclusion criteria.

Study Inclusion Criteria	Study Exclusion Criteria
Participants must be adults (>18 years of age).	Participants have a severe diagnosed psychiatric comorbidity (e.g., schizophrenia or bipolar disorder), a severe physical disability/comorbidity, traumatic brain injury, or a neurodegenerative disease.
Participants must be human (no preclinical/animal studies).	
Most participants (excluding HC) must have an illicit opioid addiction (e.g., heroin or opium) defined by either attachment to treatment services or formal diagnosis.	
Studies must use fMRI to measure connectivity.	Studies investigating one-off opioid exposure/overdose.
Publications must be in the English language.	
Studies must be original research articles. Accepted study designs include both experimental (e.g., Randomised Controlled Trials) and observational (e.g., cohort, case-control) study designs.	
Both peer reviewed and pre-print articles were screened. All articles in the final sample were peer reviewed as all pre-prints were excluded based on other exclusion criteria.	Articles not available in full text.
The study must quantify changes in connectivity as a result of abstinence or an intervention applied to the opioid using group, such as a task administered either in or out of scanner, or a pharmacological or psychological manipulation.	
The study must include both HC and HD.	

Table 2

Study information. Abbreviations: RCT=Randomised Control Trial; OST=Opioid Substitution Therapy; MMT=Metadone Maintained Therapy; CRT=Cue Reactivity Task; FC=Functional Connectivity; rTMS=randomised Transcranial Magnetic Stimulation; PPI=psychophysiological interaction; Corr=Correlation; ICA=Independent component analysis; GC=Granger Causality; DCM=Dynamic Causal Modelling; PA=Protracted Abstinence; SN=Salience Network; ECN=Executive Control Network; DMN=Default Mode Network.

Study #	Authors	Study design	Study site	# HD	Opioid use diagnostic criteria	OST (e. g., MMT)	# HC	Mean age $\pm$ std	% male	Intervention or abstinence	Type of FC method	Method of region definition	Main finding
1	Wei et al. (2021)	Cross- sectional	China	40	DSM-IV	MMT	16	HD = 36 $\pm$ 8 HC= 34 $\pm$ 7	HD = 100HC= 100	CRT and abstinence	PPI	Peak voxelwise activity: CRT	Stronger intra-DMN FC in PA vs OST HD groups
2	Liu et al. (2011)	Cross- sectional	China	16	DSM-IV	MMT	16	HD = 37 $\pm$ 7 HC= 37 $\pm$ 7	HD = 100HC= 100	CRT, abstinence.	Corr	Peak voxelwise activity: CRT	Lesser medial frontal gyrus degree in HD vs HC. Greater ACC degree in HC vs HD. Degree was correlated with cue-related activity and craving scores
3	Chen et al. (2021)	Cross- sectional	China	70	DSM-IV	No	46	HD = 34 $\pm$ 6 HC= 34 $\pm$ 8	HD = 100HC= 100	Abstinence	Pearson Corr	ICA	Stronger SN-ECN and SN-DMN FC in HC vs HD.
4	Chen et al. (2022)	Cross-sectional	China	53	DSM-IV	MMT	44	HD = 35 $\pm$ 7 HC= 32 $\pm$ 6	HD = 100HC= 100	Abstinence	Pearson Corr	ICA	Stronger SN-ECN FC in HC vs short-term abstinent HD. Stronger SN-ECN FC in long- vs short-term abstinent HD.
5	Xu et al. (2021)	Cross-sectional longitudinal	China	40	DSM-5	No	22	HD = 43 $\pm$ 8 HC= 41 $\pm$ 8	HD = 58 HC= 69	Abstinence	Pearson Corr	Atlas	Stronger FC and decreased craving in HD after abstinence
6	Lu et al. (2022)	Prospective cohort	China	53	DSM-5	No	39	HD = 42 $\pm$ 7 HC= 41 $\pm$ 9	HD = 53 HC= 64	Abstinence	Pearson Corr	Atlas	Stronger medial OFC-NAc FC and decreased craving in HD after abstinence
7	Zhang et al. (2022)	Longitudinal	China	18	DSM-5	No	30	HD = 43 $\pm$ 8 HC= 39 $\pm$ 8	HD = 39 HC= 63	Abstinence	GC	Peak voxelwise activity: CRT	Stronger EC dIPFC-insula in HD vs HC and decreased craving in HD after abstinence
8	Zhang et al. (2022)	Prospective longitudinal cohort	China	40	DSM-5	No	40	HD = 42 $\pm$ 6 HC= 41 $\pm$ 9	HD = 70 HC= 65	Abstinence	Group ICA	Sliding window	Abstinence strengthened SN-ECN and SN-DMN FC in HD
9	Li et al. (2018)	Prospective cohort	China	50	DSM-IV	MMT	20	HD = 36 $\pm$ 7 HC= 35 $\pm$ 7	HD = 100HC= 100	Abstinence	Corr	Group ICA	Weaker FC between in HD vs HC between ECN-DMN was associated with a greater number of relapses
10	Wang et al. (2021)	Cohort	China	57	DSM-IV	MMT	57	HD = 39 $\pm$ 48; HC= 36 $\pm$ 9	HD = 100HC= 100	Abstinence	Corr	Peak differences in voxelwise degree centrality	Weaker baseline HD subcortical-SN and ECN FC is associated with greater likelihood of relapse
11	Xue et al. (2022)	Cohort	China	68	DSM-IV	MMT	42	HD = 34 $\pm$ 6 HC= 34 $\pm$ 8	HD = 100HC= 100	Abstinence	Pearson Corr	Differences in voxelwise regional homogeneity	No significant differences in FC
12	Jin et al. (2023)	Intervention-al trial	China	30	DSM-5	MMT	30	HD = 47 $\pm$ 7 HC= 49 $\pm$ 6	HD = 80 HC= 93	rTMS	Corr	Group ICA	TMS strengthened ECN-DMN HD FC; weakened DMN-cortical HD FC
13	Jin et al. (2022)	RCT	China	46	DSM-5	MMT	22	HD = 46 $\pm$ 6	HD = 100HC= 100	rTMS	Corr	Group ICA	TMS strengthened DMN-cortical HD FC

(continued on next page)

Table 2 (continued)

Study #	Authors	Study design	Study site	# HD	Opioid use diagnostic criteria	OST (e.g., MMT)	# HC	Mean age $\pm$ std	% male	Intervention or abstinence	Type of FC method	Method of region definition	Main finding
14	Schmidt et al. (2015)	RCT	Switzerland	22	ICD-10	Diaph-in	17	HC= 48 $\pm$ 6 HD = 41 $\pm$ 7 HC= 42 $\pm$ 3	HD = 64 HC= 76	Acute heroin	DCM	Atlas	Heroin weakened HD subcortical-cortical FC
15	Schmidt et al. (2015)	Cross-sectional	Switzerland	20	ICD-10	Diaph-in	20	HD = 41 $\pm$ 7 HC= 40 $\pm$ 11	HD = 60 HC= 70	Acute heroin	Dual regression	Group ICA	Heroin strengthened HD intra-subcortical FC
16	Denier et al. (2015)	Cohort	Switzerland	29	Minimum 6 of months MMT	Diaph-in	20	HD = 42 $\pm$ 6 HC= 40 $\pm$ 11	HD = 72 HC= 70	Acute heroin	Corr	Atlas	Heroin weakened HD subcortical-cortical FC

activity in medial frontal gyrus, and craving scores. Conversely, the stronger FC in HD in the ACC was positively correlated with both cue-related activity in the ACC and craving scores (Liu et al., 2011).

3.3. Comparisons between HC and HD population changes in connectivity as a result of abstinence

Nine resting state studies investigated relationships between abstinence and changes in connectivity, all of which were conducted in China (Studies 3–11, Table 2). All studies included at least one HC scan for comparison to baseline and post-abstinence scans in HD. All studies included two scanning sessions for HD: one at baseline, and a second after the duration of abstinence. The duration of abstinence ranged from short (minimum = 3 days) to long term (maximum = 26 months). Moreover, the definition of abstinence varied across studies, as 5 out of 9 abstinence studies considered HD abstinent while on Opioid Substitution Therapy (OST). Despite these differences, studies consistently found HC had the strongest connectivity between nodes in the SN and ECN, followed by long-term abstinent HD, then short-term abstinent HD (Fig. 2). This pattern of stronger connectivity between SN and ECN nodes as a function of abstinence occurred in 61 % (74 out of 122 edges (i.e., connectivity between a pair of regions)) of the significant changes in connectivity associated with abstinence. Stronger ECN-SN connectivity as a function of abstinence was consistently observed across studies utilising HD maintaining abstinence with and without OST.

For example, a study by Chen et al. evaluated differences in coupling between regions in the DMN, ECN, and SN among non-OST HD with short-term (7–15 days) abstinence, long-term abstinence (6–12 months), and HC (Chen et al., 2021). HC showed significantly stronger FC between a core region of the SN, the dorsal Anterior Cingulate Cortex (dACC), to regions in both the ECN (dorsolateral Prefrontal Cortex (dlPFC)) and DMN (precuneus and Posterior Parietal Cortex (PPC)) compared with HD with long-term abstinence. HD with long-term abstinence showed significantly stronger ECN-DMN FC as compared with HD with short-term abstinence (Chen et al., 2021). A later study by the same group replicated this result in participants on short- and long-term OST-maintained abstinence. They showed long-term abstinent and HC participants had stronger FC between the dACC – dlPFC and dACC – PPC as compared with participants with short-term abstinence (Chen et al., 2022). In both studies by Chen et al., there was a significant, positive relationship between the duration of abstinence and FC strength between regions in the SN - ECN. Additionally, participants with long-term abstinence had significantly lower craving scores than participants with short-term abstinence (Chen et al., 2021, 2022).

Another study also showed significant reductions in craving scores after long-term abstinence in HD, and concurrently, significantly stronger FC in three edges: the Ventral Tegmental Area (VTA) - Orbitofrontal Cortex (OFC), VTA - ACC, and substantia nigra - OFC (Xu et al., 2021). Three additional studies reported both significant reductions in craving and significantly stronger FC or EC after abstinence (Lu et al., 2022; Zhang et al., 2022a, 2022b). Moreover, two out of three studies found a significant relationship between the abstinence-strengthened FC or EC and corresponding decreases in craving (Lu et al., 2022; Zhang et al., 2022b).

Differences in FC between HC, HD who did relapse, and HD who did not relapse have been evaluated (Li et al., 2018; Wang et al., 2021). Li and colleagues collected baseline rsfMRI scans from HD and HC, as well as the number of relapses per month over a three-month period. The authors found weaker FC between nodes in the ECN (dlPFC) and DMN (mPFC) in HD was significantly associated with a greater number of relapses. Similarly, Wang et al. collected baseline rsfMRI data from HD before they began an OST-maintained, 26-month abstinence. The authors found a significant association between the likelihood of relapse and weaker baseline FC between the Nucleus Accumbens (NAc) and regions within the SN and ECN (e.g., the Inferior Frontal Gyrus (IFG) and dlPFC, respectively) (Wang et al., 2021). One study did not find any

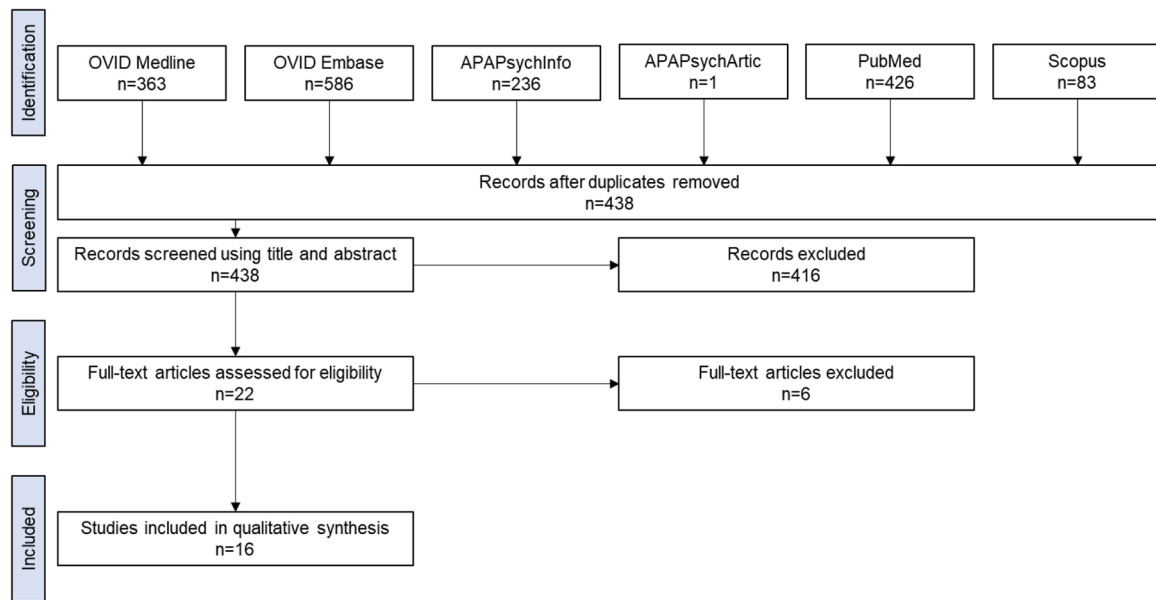


Fig. 2. PRISMA diagram outlining search strategy results and article screening process. Search terms relating to heroin or opium opioid dependence, connectivity, and fMRI were employed as provided in [Appendix 1](#) (Fig. 1). The terminology used for.

differences in FC between HD and HC (Xue et al., 2022).

3.4. Differences in pairwise resting state connectivity changes as a result of TMS between HC and HD

The effects of applying TMS to the dlPFC in HD have been investigated in two studies (Studies 12–13, [Table 2](#)). In both studies, HD had a baseline rsfMRI scan, then received randomised TMS (rTMS) to the dlPFC at 10 Hz every day for one week, after which another rsfMRI scan was collected. HC had a rsfMRI scan, but received no intervention. The HC scan was used as a comparison for the before- and after-stimulation rsfMRI scans in HD. Both studies were a part of a larger clinical trial, but it was not clear if any participants were included in both studies. Both studies employed group ICA to identify regions from the DMN, SN, and ECN used in the FC analyses. The first published study by Jin et al. showed TMS strengthened left dlPFC - left parahippocampal gyrus FC (i. e., stronger ECN-DMN connectivity), and weakened FC between the right precentral gyrus and three DMN regions: the PCC, precuneus, and IPL (Jin et al., 2022). The second study by Jin et al. showed TMS weakened FC in two edges: the left IPL - right occipital cortex, and the left IPL - left middle frontal gyrus (which is associated with attentional networks (Menon and D'Esposito, 2022; Talati and Hirsch, 2005; Jin et al., 2023)). Despite the similarity in study methods and the focus on regions in the DMN, SN, or ECN, there was no overlap in the edges showing significant changes as a result of TMS. However, both studies showed TMS strengthened FC between regions in the DMN to areas in sensory cortices.

The relationship between TMS-induced changes in FC and measures of spontaneous and drug cue-induced craving was different in each study. The first study showed the stronger dlPFC - parahippocampal gyrus FC was negatively related with craving. In other words, the TMS-strengthened ECN - DMN FC was associated with decreased craving (Jin et al., 2022). The second study found TMS weakened FC in two DMN-SN edges (the IFG - IPL, and IFG - PCC) related to reductions in craving (Jin et al., 2023).

3.5. Differences in pairwise resting state connectivity changes as a result of acute heroin exposure between HC and HD

Three studies, all of which were conducted by the same group based

in Switzerland, investigated the effects of acute heroin administration on connectivity in HD (Studies 14–16, [Table 2](#)). HD connectivity before and after the acute administration of heroin was compared with connectivity in HC, who received a placebo/vehicle instead of heroin. All HD must have received heroin-assisted treatment for at least 6 months, with a stable dose for at least 3 months. Two studies administered heroin hydrochloride and collected data during resting state only, whereas in the third, participants also viewed a series of faces with fearful or neutral expressions after heroin dosing. In all studies HD were administered their prescribed dose of heroin hydrochloride in 5 ml of sterile water through an intravenous catheter over 30 seconds. Then, 20 minutes after injection, HD participants performed the MRI scan.

There were no consistent effects of acute heroin administration on connectivity in HD, nor consistent differences in connectivity between HD and HC. For example, one of the studies showed that in HD, heroin administration strengthened FC between the putamen and the basal ganglia/limbic regions (Schmidt, Denier, et al., 2015). Conversely, a study by Denier et al. showed heroin weakened FC between the thalamus and several regions, including the precuneus, lateral occipital cortex, superior parietal lobule, middle temporal gyrus, and medial frontal gyrus (Denier et al., 2015).

The study by Denier et al. showed most of the significant differences in FC were not between HD and HC, but rather between pre- and post-heroin administration in HD. HC had stronger FC between the thalamus and four regions: the precuneus, lateral occipital cortex, middle temporal gyrus, and the precentral gyrus. A different relationship was present in the study by Schmidt et al., which showed HC had stronger FC between the PCC/precuneus and the basal ganglia/limbic network compared with HD at baseline. This difference was abolished under the influence of heroin (Schmidt et al., 2015a). Administration of heroin also removed differences in DCM between HC and HD during an emotional face processing task (Schmidt et al., 2015b). During the presentation of faces with fearful expressions, heroin administration attenuated the significantly stronger FC in HD pre-administration of heroin vs HC. The weakened FC was between two edges: the left fusiform gyrus - left amygdala, and the right amygdala - right OFC.

4. Discussion

An improved mechanistic understanding of how neural processes

shape opioid addiction, and how they can be attenuated, informs the development of therapies for opioid addiction. This review intended to develop a better understanding of connectivity as a neural correlate underpinning opioid addiction. We assessed whether abstinence or interventions affects HD connectivity, and if changes in connectivity relate to craving or likelihood of relapse.

We found that HD show differences in connectivity from HC at baseline. These differences typically consist of weaker connectivity between regions in the ECN, SN, and DMN (Fig. 3). Each of these networks are responsible for a key aspect of healthy brain function. Previous work has shown opioid addiction disrupts DMN, ECN, and SN network function and the processes they mediate. For example, HD have different activity patterns than HC in DMN regions (Pandria et al., 2018; Zhang et al., 2011). DMN regions include the following: mPFC, angular gyrus, superior frontal gyrus, lateral temporal lobes and cortex, temporal junction and pole, the hippocampus, parahippocampal cortex, retrosplenial cortex, PCC, precuneus, and IPL (Spreng and Andrews-Hanna, 2015). A review of HD vs HC resting state activity related differences in DMN regions to deficits in self-referential processing, emotional regulation, and autobiographical memory (Pandria et al., 2018). HD also exhibit cognitive deficits and atypical function in core ECN regions such as the dlPFC, pre-supplementary motor area and PPC (Lee et al., 2005; K. Shen et al., 2020; Tanabe et al., 2019). The SN includes the right IFG, anterior insula, and the dACC (Menon and Uddin, 2010; Peters et al., 2016). The SN is responsible for the detection of salient stimuli and recruitment of either the DMN or ECN, depending on whether internally-relevant or externally-focused processes is most appropriate, respectively (Menon, 2011). Impairments in the SN's ability to coordinate DMN and ECN function is associated with deficits reported in HD (Chen et al., 2022; Jin et al., 2022; Li et al., 2018, p. 201). For example, deficits in the SN's ability to mediate a shift between DMN-controlled internal processes and ECN-mediated, executive control processes impairs goal-directed behaviour (Uddin et al., 2019). Moreover, the rumination and impaired self-awareness in HD are associated with dysfunctional interactions between the DMN, ECN, and SN (Killingsworth and Gilbert, 2010; Zhang and Volkow, 2019).

While most HD participants showed weaker baseline connectivity between the DMN, ECN, and SN than HC, studies consistently reported that abstinence strengthened connectivity between key regions in the ECN (e.g., dlPFC) and DMN (e.g., IPL) (Yuan et al., 2010), and that abstinence strengthens connectivity among DMN, ECN, or SN regions in the direction towards HC (Yang et al., 2022; Zhang et al., 2022b) (Fig. 4). Additionally, abstinence was shown to relate to reductions in craving and strengthened connectivity among reward areas (Lu et al., 2022; Xu et al., 2021), and from reward areas to SN (Wang et al., 2021; Xu et al., 2021) and ECN (Wang et al., 2021) (Fig. 4).

The consistency of the effect of abstinence on connectivity in HD is notable since studies utilising both OST- and non-OST-supported abstinence were included in this work. OST-supported abstinence is different from opioid-free abstinence. OST has been proposed to maintain the hypodopaminergic state/trait in HD (Blum and Baron, 2019) which contributes to aberrant, reward-related neural processes associated with addiction. Given that both OST- and non-OST-supported abstinence tended to strengthen HD connectivity towards that seen in HC, stability in opioid use may relate to a “normalisation” of connectivity patterns. In turn, the stability-associated changes in connectivity may relate to reductions in craving and relapses (Fig. 5).

Similar to the effects of abstinence on connectivity and craving/relapse, studies showed that TMS strengthened FC of ECN, SN, and DMN regions in HD towards HC, which related to decreased craving and relapse (Fig. 4). While the evidence supporting a clinically relevant relationship between craving and relapse is unclear (Hasin et al., 2013; Tiffany and Wray, 2012), the effects of abstinence on craving and relapse reviewed here (Li et al., 2018; Wang et al., 2021) suggest that reduced craving is associated with reduced likelihood of relapse. This aligns with work showing decreased craving reduces the risk of relapse in HD (Saraiya et al., 2021; Tsui et al., 2014), and that stronger connectivity among the ECN, SN, and DMN predicted lower risk of relapse in people with opioid, cocaine, methamphetamine, nicotine, and alcohol addiction (Moeller and Paulus, 2018).

The effects of TMS on craving reviewed here also accord with other investigations of the effects of TMS on craving in HD (Li et al., 2021; Liu

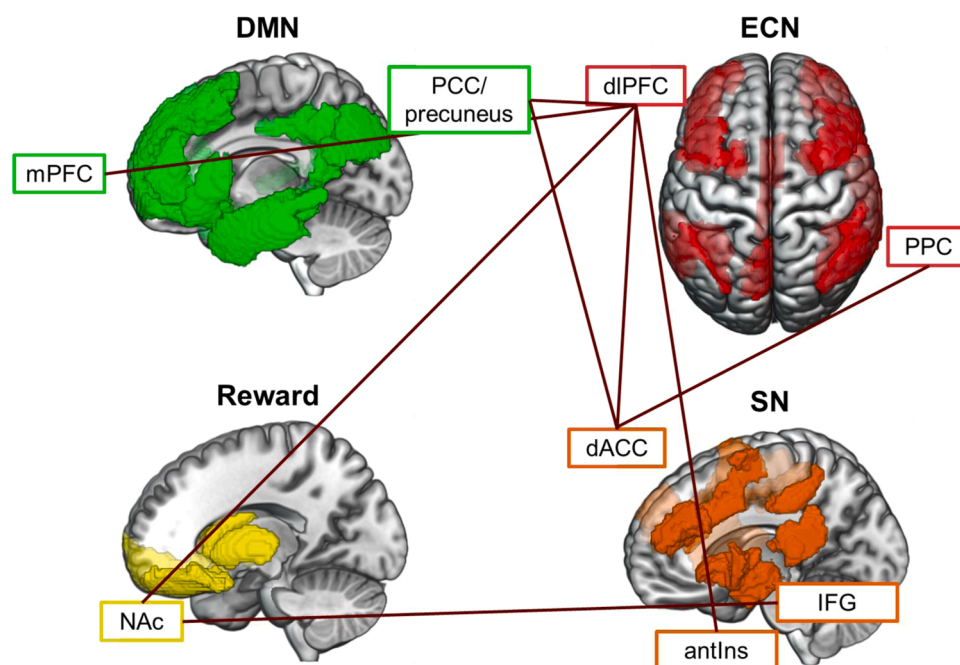


Fig. 3. Edges where abstinence significantly strengthened connectivity in the direction towards HC. Edges (i.e., connections between two regions\') were selected that had replicable relationships across at least two studies and are grouped according to the functional network in which they were categorised. Abbreviations are as follows: mPFC = medial Prefrontal Cortex; PCC = Posterior Cingulate Cortex; dlPFC = dorsolateral Prefrontal Cortex; PPC = Posterior Parietal Cortex; IFG = inferior frontal gyrus; antIns = anterior insula; dACC = dorsal Anterior Cingulate Cortex; NAc = Nucleus Accumbens.

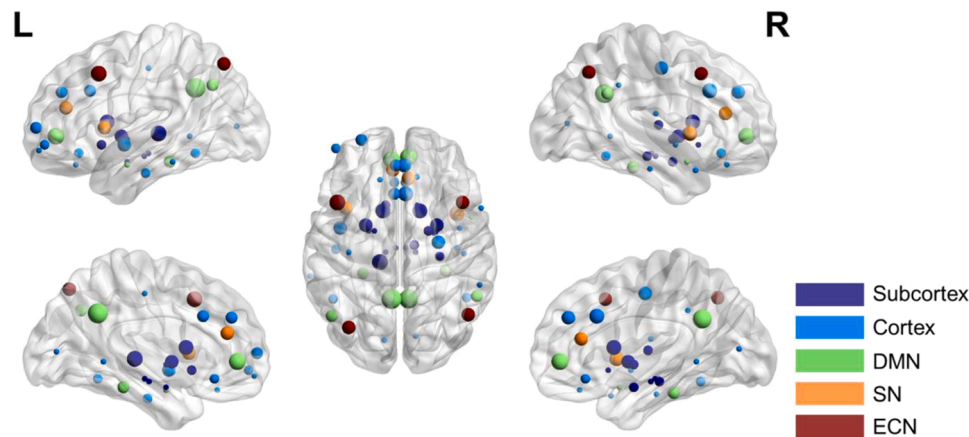


Fig. 4. Glass brains showing ROIs with different connectivity between HC and HD as a result of an abstinence, TMS, or acute opioid exposure. The size of the region scales with the number of times it was mentioned across studies. The colour of each region indicates whether a study grouped it within the DMN, SN, or ECN. All other regions were grouped into subcortical or cortical groups. This figure was made using BrainNet (Xia et al., 2013).

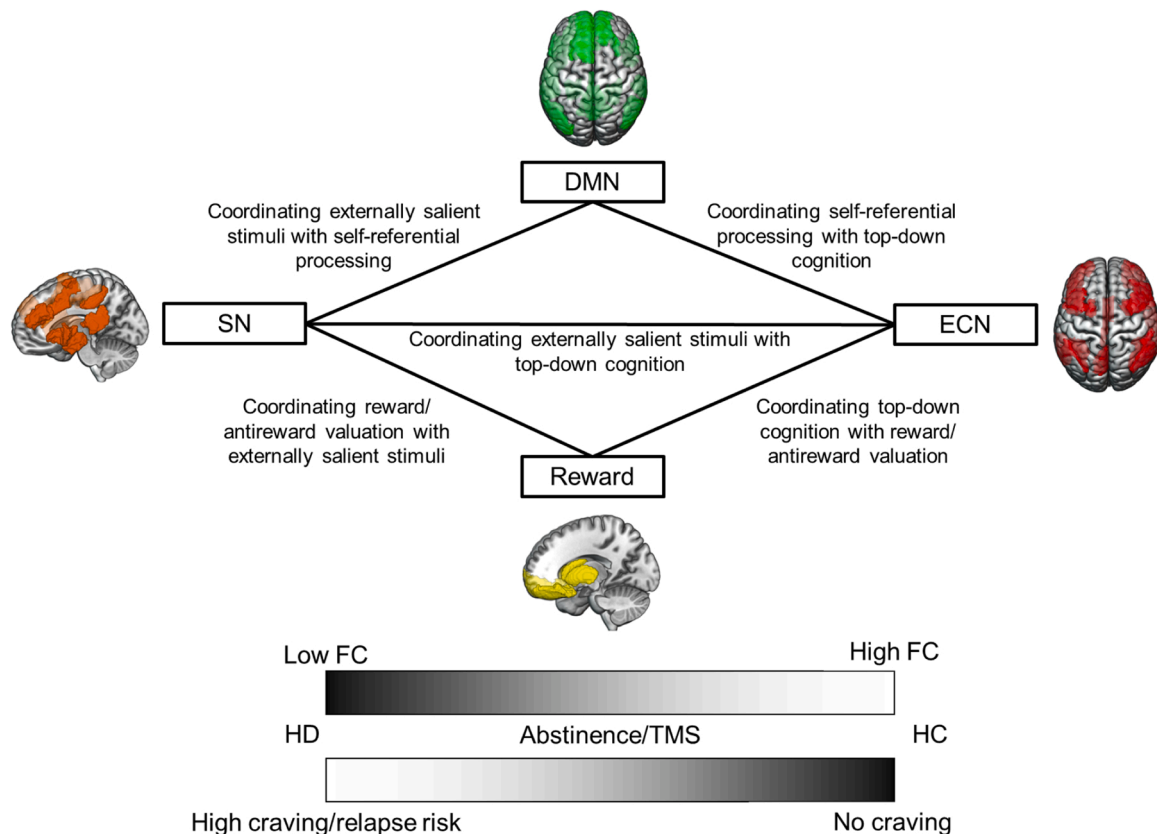


Fig. 5. Schematic of how weakened between-network connectivity relates to deficits in processes mediated by between-network connectivity. The weak FC and high craving/risk of relapse in active users are shown as the black and white extremes on the left side of the top and bottom bars at the bottom of the figure, respectively. To demonstrate how abstinence or TMS is associated with increased FC, the colour of the top bar shifts from black, to grey, to white. The lower bar visualises the corresponding decrease in craving and risk of relapse as a shift from white, to grey, to black.

et al., 2020; Shen et al., 2016). However, a study investigating whether TMS of the dlPFC reduces craving in HD did not show a reduction in craving (Tsai et al., 2021). While a review posited this discrepancy was due to the inclusion (Tsai et al., 2021) or exclusion (Li et al., 2021; Liu et al., 2020; Shen et al., 2016) of participants on OST (Mehta et al., 2024), the two studies reviewed in this work showing TMS-induced reductions in craving included participants on OST (Jin et al., 2022, 2023). Moreover, another review of the effects of neuromodulation on craving in opioid addiction included three TMS studies (Ward et al.,

2020), two of which had not been included in the review by Mehta et al. While neither study reported whether their study in- or excluded participants on OST, and one study did not target the dlPFC (Shen et al., 2017), both studies showed decreases in craving following TMS (Sahlem et al., 2017; Shen et al., 2017). While no studies evaluating the effect of other noninvasive brain stimulation (NIBS) modalities were eligible for inclusion in this work, research has shown similar relationships between tDCS and reduced craving. A review on the effects of tDCS in neuropsychiatric disorders found administering tDCS with the anode on the

right dlPFC, and the cathode over the left dlPFC, consistently decreased craving (but not relapse rates) in people with OUD who were on methadone (Nakamura-Palacios et al., 2021). While replicability across neuromodulation studies is often low due to high experimenter and interindividual variability (Guerra et al., 2020; Li et al., 2015), the post-TMS reduction in craving in HD shown in seven out of eight TMS studies, as well as across tDCS research, encourages further exploration of TMS as a method to reduce craving and relapse.

4.1. Urge and action framework: bridging connectivity, neurobiological models of problematic drug use, and therapeutic strategies to maintain abstinence

An interim summary is that HD typically have lower between-network connectivity as compared to HC, that both abstinence and TMS increase connectivity, which relates to decreased craving and risk of relapse. Yet, it remains unclear **why** decreased between-network connectivity is associated with craving and relapse. One putative mechanism is the “urges-to-actions trajectory” proposed in a review assessing the use of NIBS for substance dependence and Major Depressive Disorder (Dunlop et al., 2017). The urges-to-actions trajectory suggests that incentive drives (mediated by reward/antireward networks) initiate goal formation (through the DMN), culminating in consumption (attributed to cognitive and somatomotor networks). Therefore, abstinence- or TMS-increased inter-network connectivity may represent an increased ability to shift neural resources away from the urges-to-actions trajectory. This aligns with current therapeutic strategies to support abstinence. For example, SMART Recovery (<https://smartrecovery.org.uk/>) utilises DEADs approach to identify strategies to cope with drug cravings and urges. DEADs is an acronym for Deny/Delay giving in to the urge; Escape the trigger of the urge, Avoid, accept, or attack the trigger of the urge, Distract the urge with an activity, and Substitute for addictive thinking. This approach is an example

of how SMART Recovery and other therapeutic models (e.g., Cognitive Behavioural Therapy and Dialectical Behavioural Therapy) develop skills to identify urges, understand their origin, and utilise cognitive and behavioural strategies to maintain abstinence. Developing these skills can be conceptualised as the intentional utilisation of the neural resources necessary to identify cravings or urges, and through introspection, cognition, and redirection, avoid relapse. Given that these neural resources consist of brain regions and networks, it then follows that **low connectivity between networks might impede the ability to utilise therapeutic strategies to maintain abstinence when urges or cravings arise.**

We have adapted the urges-to-actions trajectory to incorporate results from this review and therapeutic strategies to maintain abstinence (Fig. 6). First, we shift from a linear trajectory, where each stage corresponds to a network, to a factor-based framework. Factors are modelled after SMART Recovery, CBT, and DBT approaches that identify the thoughts and feelings surrounding cravings. Factors are presented separately (i.e., not connected in a line) to represent how the number and weights of factors contributing to relapse varies across people and contexts. The boxes underneath each factor translate the clinically relevant language of factors to neurobiology. Each box represents a neurobiological model or process affected by HD, and lists brain regions associated with the model or process. Since each brain region is also associated with a functional network, boxes are shaded to link functional networks with neurobiological models or processes affected by HD. Collectively, our adapted urge and action framework links clinically relevant factors contributing to relapse with their neural underpinnings. We utilised coloured boxes to show how brain regions are associated with both functional networks, neurobiological models, and processes affected by HD, and substance dependence more broadly. This provides context for how the results observed in this review – lower between-network connectivity in HD vs HC – relates to clinically relevant factors of craving and relapse. While outside the scope of this work, further

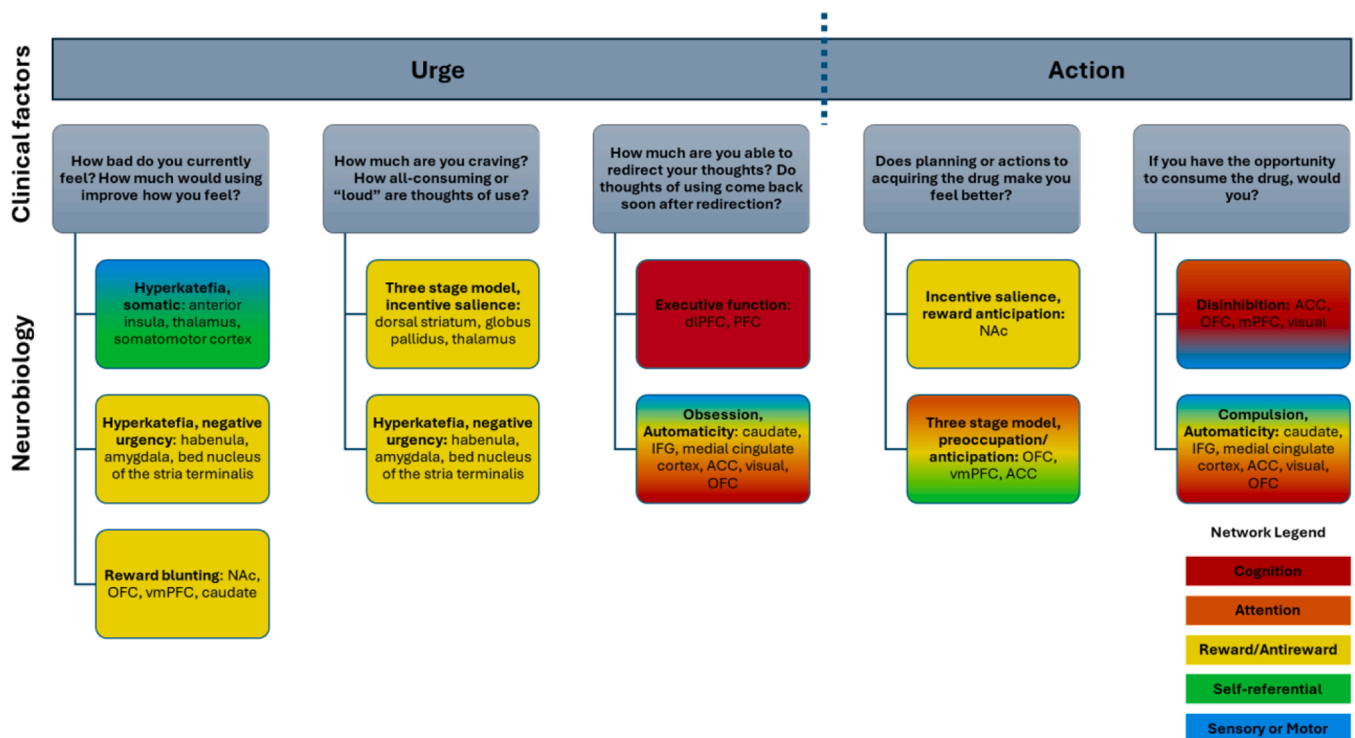


Fig. 6. An urge and action framework adapted from Dunlop et al.'s urges-to-actions trajectory (Dunlop et al., 2017). The framework is grounded in five factors that contribute to craving and relapse. Underneath each factor is related to two or three boxes. The bold text in each box summarises a model of processes impacted by substance dependence. Each process is accompanied by the brain regions with which processes are typically associated. The functional networks that brain regions are associated with determine the colour of each box.

development of the urge and action framework can link each factor with therapeutic strategies (e.g., introspection, imagery, redirection, noninvasive brain stimulation (NIBS), etc) and their neural underpinnings.

4.2. Experimental design and analyses methods influence connectivity results

Most studies reviewed in this work utilised regions of interest contained in one of three networks – the ECN, DMN, and SN. Therefore, interpretations of how connectivity differences between HD and HC related to clinical metrics focused on processes governed by those networks. However, interpretations that do not consider the many-to-many, context-dependent role of brain regions are limited (Cole et al., 2013; Matthews and Hampshire, 2016; Medaglia et al., 2015; Soreq et al., 2019). For example, the mPFC is considered a core region of both the DMN and reward networks. During rest, the mPFC's function will be associated with other DMN regions, whereas during a reward-related task, it will be associated with regions in reward networks (Spreng and Andrews-Hanna, 2015; Tzschentke, 2000; van Holstein and Florresco, 2020). Yet, the mPFC was only considered as a DMN region in the studies included in the review. It would have been informative to see analyses investigating whether the mPFC had stronger connectivity to other regions in the DMN or reward-related networks. Such an analysis would enable greater sensitivity in characterising whether the role of the changes in mPFC connectivity are associated with either self-referential (e.g., DMN-related) or reward processes disrupted by opioid addiction. We encourage future research to consider the diverse functions of brain regions when interpreting connectivity results. Such interpretations can be aided by reviews that comprehensively characterise the role of regions central to processes affected by HD, or substance (mis)use/dependence. For example, one review considered how the various functions of the insular cortex, which include reward representation, cognitive control, and interoception, contributed to the positive relationship between abstinence, increased insular connectivity, and decreased craving (Yang et al., 2022). Similar region-centric approaches have been taken for the habenula (Curtis et al., 2017) and nucleus accumbens (Tolomeo et al., 2022). Our adapted urge and action framework (Fig. 6) enables incorporation of research characterising the neural correlates of HD using both network and regional approaches.

Another limitation associated with regions of interest is when brain regions are defined using standard atlas parcellations (Box 2). Brain atlases are typically created using HC and may not adequately capture how state- and trait-like features of HD change the topology (i.e., the spatial organisation) of functional networks. Incorrect assignment of voxels or brain regions to a network introduces confounds in study results and their interpretation. One way to overcome this limitation is to use precision mapping of functional network topology (Kong et al., 2019, 2021; Rosvall and Bergstrom, 2008). This individualised approach to assigning voxels or brain regions to functional networks works by using neuroimaging data to redefine boundaries of functional networks. This approach was successfully utilised in a recent study showing that expansion of a frontostriatal network is a trait-like feature of Major Depressive Disorder, and within-network connectivity was predictive of clinically relevant metrics of depression (Lynch et al., 2024). The work by Lynch et al. is notable for its initial use of precision functional mapping in a “deep dataset” (e.g., multi-session, longitudinal data) of people with Major Depressive Disorder. However, when precision functional mapping was applied to large, single-session datasets, the results of trait-like frontostriatal network expansion in people with Major Depressive Disorder were replicated (Lynch et al., 2024). The ability to utilise single-session datasets greatly facilitates the application of precision functional mapping to HD data and its relationship to clinical metrics. For example, studies reviewed in this work could more accurately assess differences in network size and connectivity between HD and HC, and how these differences relate to measures of craving or relapse. These differences can be validated through replicating the

analysis on large datasets, such as the ENIGMA addiction working group (<https://www.enigma-brain.org/main/index.html%3Fp=1611.html>).

It was notable that all studies investigating the effects of abstinence or acute opioid administration on connectivity were conducted in either China or Switzerland, respectively. Studies conducted solely in one country may not be representative of the broader population (Ge et al., 2023; Han and Northoff, 2008; Kitayama and Salvador, 2017). For example, abstinence programs that differ across countries may introduce variability in the neural markers of abstinence. Some countries (e.g., China) utilise compulsory isolated treatment, whereas other countries (e.g., US, UK) typically do not (National Institute for Health Care and Excellence, 2007; Tibke, 2017). Similarly, the administration of heroin was in line with Switzerland's therapeutic strategy for HD, which utilises pharmaceutical heroin diacetylmorphine (DAM). While these studies align with clinical practice in Switzerland, it is important to conduct more international research on the neural correlates of addiction and their response to treatment. Such work would substantiate whether strengthened connectivity is a suitable biomarker of responses to treatment for opioid addiction.

The methods employed in a study impact results and interpretation (Box 1, Box 2). While most studies evaluating the effect of abstinence on connectivity in HC and HD defined their regions using standard functional or anatomical parcellations, three studies (Wang et al., 2021; Wei et al., 2021; Xue et al., 2022) chose regions based on the presence of statistically significant differences in: regional homogeneity between HC, short, and long-term abstaining people with OUD (Xue et al., 2022), voxelwise differences in Degree Centrality or BOLD activity between HC and OUD participants (Wang et al., 2021), and voxelwise activity when viewing heroin vs neutral cues (Wei et al., 2021). The purpose of selecting regions of interest based on voxelwise measures of significance is to narrow the scope of analysis within the vast quantity of data generated by fMRI. However, this practice is referred to as “double-dipping”, and is a form of circular analysis (Kriegeskorte et al., 2009). Circular analyses often occur in large, noisy datasets (e.g., fMRI data), where a selection of the data that is significant in one analysis is used in subsequent statistical tests. The noise contained in the first analysis is amplified in the second, increasing the likelihood of a type I error, i.e., a false positive. To avoid this issue, it is recommended to use independent study populations, or better yet, meta-analysis, to identify regions of interest (Box 1). ICA-derived regions are another robust way to focus analyses on regions shown to be reliably engaged in the condition (e.g., task or resting state) of interest without assuming statistical differences between groups (Duff et al., 2012). To summarise, the parcellation method by which regions of interest are selected is an important part of connectivity analyses and may influence the quality of results. Readers are advised to consult Kriegeskorte's guidelines on selecting regions of interest to reduce the impact of noise and bias in their results (Kriegeskorte et al., 2009).

Another methodological comment concerns the disparity in clinical factors (e.g., sex, socioeconomic status, neurodiversity) in study populations. For example, nearly half of the studies in this review only included men. There is some literature showing connectivity differences between HC males and females (Weis et al., 2020), and there are some sex-based differences in the functional correlates of addiction (Nicolas et al., 2022; Smith et al., 2023). Similar effects of neurodiversity and socioeconomic status on connectivity have been reported (Horien et al., 2023; Sripada et al., 2021; Yapple and Yu, 2020). Therefore, future work should endeavour to include representation of male and female participants, as excluding the consideration of clinically relevant factors from research negatively impacts the clinical relevance of findings (Johnson et al., 2014).

4.3. Future directions

One of the main takeaways from this review is that people with HD consistently show weaker between-network connectivity as compared to

HC, and that abstinence or TMS both attenuates this difference and improves clinically relevant metrics of HD. These results encourage further investigation as to whether decreased between-network connectivity is a biomarker of HD. However, reliable biomarkers of HD or any other psychiatric condition would not be utilised in current diagnostic approaches. In the UK, HD is diagnosed using the DSM, which defines the prevalence and severity of a disorder based on the number and duration of symptoms. The limitations in symptom-based diagnoses are well documented (Cooper and Balsis, 2009; Lane and Sher, 2015) and have driven recent calls for biologically informed diagnosis and treatment of SUDs (Kas et al., 2025). One solution is the Research Domain of Criteria (RDoC) framework, which classifies psychiatric conditions using a combination of pathophysiological markers underpinning transdiagnostically relevant domains (Insel et al., 2010). A recent systematic review provides an example of how the RDoC framework can integrate research findings into a cohesive, neurobiologically informed understanding of SUD (Rezapour et al., 2024). The authors mapped the therapeutic targets/strategies of randomised control trials of person-centred interventions to prevent the development of SUD in adolescents into RDoC domains, and assessments of the intervention's efficacy into RDoC units of analysis. This review facilitates future research quantifying the relationship between the severity of SUD and neuroimaging biomarkers shared among adolescents at risk of developing SUD, adults with SUD, and adults and other psychiatric conditions. Such research should utilise large datasets with neuroimaging and clinically relevant data, such as the (Adolescent Brain Cognitive Development) (ABCD) (Casey et al., 2018) and ENIGMA addiction working group (<https://www.enigma-brain.org/main/index.html%3Fp=1611.html>).

Not only does elucidating the transdiagnostic neurobiological underpinnings of HD develop a mechanistic understanding of HD and improve diagnostic capabilities, but it also sheds insight as to where therapeutic interventions can be effectively deployed. NIBS is a prime example of a single therapeutic intervention able to target personalised neuroimaging-informed biomarkers that effect a range of transdiagnostic symptoms (Dunlop et al., 2017). Indeed, another purpose of the urge and action framework was to identify stages where administering NIBS would be most effective. The authors of the original urge-to-action trajectory noted that NIBS for both MDD and substance dependence is typically applied to the dlPFC, to interfere with the cognitive processes underpinning planning and actions related to drug consumption (Dunlop et al., 2017). However, it may be more effective to intervene in an earlier stage of the pathological urges-to-actions trajectory, such as the formation of incentive drives. The authors acknowledged that, at the time, conventional NIBS could only target superficial cortical regions. As such, regions associated with reward/anti-reward processes were largely inaccessible. Recent advances in two NIBS modalities, Temporal Interference (TI) stimulation Low-intensity Focused Ultrasound (LIFU), overcome the targeting limitations of NIBS. TI stimulation is a form of tACS that can modulate task-relevant activity and connectivity in the hippocampus (Grossman et al., 2017; Violante et al., 2023). LIFU has been more extensively researched as a therapy for HD. Administering LIFU to a portion of the NAc defined by its engagement during an individualised cue-reactivity paradigm substantially decreased craving and substance use in HD (Mahoney, Haut, et al., 2023; Mahoney, Thompson-Lake, et al., 2023). The second advancement made by the work of Mahoney and colleagues is the application of personalised stimulation. Personalised stimulation has been suggested as a strategy to overcome the interindividual variability in the brain and behavioural effects of NIBS (Bansal et al., 2018; Kurtin et al., 2023; Li et al., 2015; Menardi et al., 2022). Our urge and action framework can be utilised in conjunction with a recommended approach for identifying personalised NIBS parameters (Kurtin et al., 2023).

In summary, we advocate that future research investigates the transdiagnostic relevance of neuroimaging informed biomarkers of HD.

One approach is to utilise large neuroimaging datasets; another approach is to administer personalised NIBS. Personalised NIBS aligns with calls from the research community in substance dependence to utilise transdiagnostic, biomarker-informed therapeutic interventions (Kas et al., 2025), and from the NIBS community to overcome interindividual variability in the effects of NIBS on brain function and behaviour (Polania et al., 2018; Toth et al., 2024).

4.4. Conclusions

There is a pressing need to characterise the mechanisms of addiction and develop therapies that attenuate them. Connectivity can extend the insights garnered by activity-based analysis and identify a clearer link between targets for therapeutic interventions and the quantification of the therapies' success. This work suggests that either abstinence or TMS changes connectivity in HD in the direction of HC, which in turn, relates to reduced craving and risk of relapse. Improving the methodological practices and widening the distribution of research conducted in this field will not only strengthen the robustness of these findings, but also facilitate the application of connectivity analyses to translational research and clinical practice.

Appendix

Search strategies

PubMed

("functional connectivity"[Title/Abstract] OR "functional magnetic resonance imaging"[Title/Abstract] OR "fMRI"[Title/Abstract] OR "functional imaging"[Title/Abstract] OR "functional-magnetic"[Title/Abstract] OR "connectivity"[Title/Abstract] OR "connectome"[Title/Abstract]) AND ("oud"[Title/Abstract] OR "use disorder"[Title/Abstract] OR "addiction"[Title/Abstract] OR "addict*"[Title/Abstract] OR "dependen*"[Title/Abstract] OR "behavior, addictive"[MeSH Terms] OR "addiction medicine"[MeSH Terms] OR "substance related disorders"[MeSH Terms] OR "substance abuse, intravenous"[MeSH Terms] OR "substance abuse, oral"[MeSH Terms] OR "opiate substitution treatment"[MeSH Terms]) AND ("opiu*"[Title/Abstract] OR "heroin"[Title/Abstract] OR ("illicit drug"[Title/Abstract] OR "illicit drugs"[MeSH Terms]) AND "opio*"[Title/Abstract]) OR "opium"[MeSH Terms] OR "heroin"[MeSH Terms] OR "heroin dependence"[MeSH Terms] OR "opium dependence"[MeSH Terms])

OVID: MEDLINE, EMBASE, PsycINFO, PsycArticlesFullText

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((TITLE(oud) OR ABS(oud) OR TITLE("use disorder") OR ABS("use disorder") AND TITLE(addic*) OR ABS(addic*) OR TITLE(dependen*) OR ABS(dependen*))

Data availability

No data was used for the research described in the article.

References

- Allen, J.S., Bruss, J., Mehta, S., Grabowski, T., Brown, C.K., Damasio, H., 2008. Effects of spatial transformation on regional brain volume estimates. *Neuroimage* 42, 535–547. <https://doi.org/10.1016/j.neuroimage.2008.05.047>.
- Amunts, K., Zilles, K., 2015. Architectonic mapping of the human brain beyond Brodmann. *Neuron* 88, 1086–1107. <https://doi.org/10.1016/j.neuron.2015.12.001>.
- Bansal, K., Nakuci, J., Muldoon, S.F., 2018. Personalized brain network models for assessing structure–function relationships. *Curr. Opin. Neurobiol.* 52, 42–47. <https://doi.org/10.1016/j.conb.2018.04.014>.
- Baumgartner, R., Windischberger, C., Moser, E., 1998. Quantification in functional magnetic resonance imaging: Fuzzy clustering vs correlation analysis. *Magn. Reson. Imaging* 16, 115–125. [https://doi.org/10.1016/S0730-725X\(97\)00277-4](https://doi.org/10.1016/S0730-725X(97)00277-4).
- Belin, D., Belin-Rauscent, A., Murray, J.E., Everitt, B.J., 2013. Addiction: failure of control over maladaptive incentive habits. *Curr. Opin. Neurobiol.* 23 (4), 564–572. <https://doi.org/10.1016/j.conb.2013.01.025>.
- Bijsterbosch, J.D., Beckmann, C.F., Woolrich, M.W., Smith, S.M., Harrison, S.J., 2019. The relationship between spatial configuration and functional connectivity of brain regions revisited. *eLife* 8, e44890. <https://doi.org/10.7554/eLife.44890>.
- Biswal, B., Zerrin Yetkin, F., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magn. Reson. Med.* 34 (4), 537–541. <https://doi.org/10.1002/mrm.1910340409>.
- Black, C. (2021). Annex for Review of Drugs Part Two: Prevention, Treatment, and Recovery. Home Office UK. (<https://assets.publishing.service.gov.uk/media/60ee f5588fa8f50c768386fd/independent-review-of-drugs-part-2-annexes.pdf>).
- Blum, K., Baron, D., 2019. Opioid substitution therapy: achieving harm reduction while searching for a prophylactic solution. *Curr. Pharm. Biotechnol.* 20 (3), 180–182. <https://doi.org/10.2174/138920102003190422150527>.
- Calhoun, V.D., Liu, J., Adali, T., 2009. A review of group ICA for fMRI data and ICA for joint inference of imaging, genetic, and ERP data. *NeuroImage* 45, S163–S172. <https://doi.org/10.1016/j.neuroimage.2008.10.057>.
- Campbell, M., McKenzie, J.E., Sowden, A., Katikireddi, S.V., Brennan, S.E., Ellis, S., Hartmann-Boyce, J., Ryan, R., Shepperd, S., Thomas, J., Welch, V., Thomson, H., 2020. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ* 368, l6890. <https://doi.org/10.1136/bmj.l6890>.
- Casey, B.J., Cannonier, T., Conley, M.I., Cohen, A.O., Barch, D.M., Heitzeg, M.M., Soules, M.E., Teslovich, T., Dellarco, D.V., Garavan, H., Orr, C.A., Wager, T.D., Banich, M.T., Speer, N.K., Sutherland, M.T., Riedel, M.C., Dick, A.S., Bjork, J.M., Thomas, K.M., Dale, A.M., 2018. The Adolescent Brain Cognitive Development (ABCD) study: imaging acquisition across 21 sites. *Dev. Cogn. Neurosci.* 32, 43–54. <https://doi.org/10.1016/j.dcn.2018.03.001>.
- Center for Disease Control and Prevention. (2022, January). Multiple Cause of Death Data on CDC WONDER. National Center for Health Statistics: Mortality Data on CDC WONDER: Provisional Multiple Cause of Death Data. (<https://wonder.cdc.gov/mcd.html>).
- Chen, J., Wang, F., Zhu, J., Li, Y., Liu, W., Xue, J., Shi, H., Li, W., Li, Q., Wang, W., 2021. Assessing effect of long-term abstinence on coupling of three core brain networks in male heroin addicts: A resting-state functional magnetic resonance imaging study. *Addict. Biol.* 26 (4), e12982. <https://doi.org/10.1111/adb.12982>.
- Chen, J., Wang, S., Li, Z., Li, Y., Huang, P., Zhu, J., Wang, F., Li, Y., Liu, W., Xue, J., Shi, H., Li, W., Liang, Z., Wang, W., Li, Q., 2022. The effect of long-term methadone maintenance treatment on coupling among three large-scale brain networks in male heroin-dependent individuals: A resting-state fMRI study. *Drug Alcohol Depend.* 238, 109549. <https://doi.org/10.1016/j.drugalcdep.2022.109549>.
- Cisler, J.M., Bush, K., Steele, J.S., 2014. A comparison of statistical methods for detecting context-modulated functional connectivity in fMRI. *NeuroImage* 84, 1042–1052. <https://doi.org/10.1016/j.neuroimage.2013.09.018>.
- Cole, M.W., Reynolds, J.R., Power, J.D., Repovs, G., Anticevic, A., Braver, T.S., 2013. Multi-task connectivity reveals flexible hubs for adaptive task control. *Article 9. Nat. Neurosci.* 16 (9). <https://doi.org/10.1038/nn.3470>.
- Conti, A., Duggento, A., Guerri, M., Passamonti, L., Indovina, I., Toschi, N., 2019. Variability and reproducibility of directed and undirected functional MRI connectomes in the human brain. *Entropy* 21, 661. <https://doi.org/10.3390/e21070661>.
- Cooper, L.D., Balsis, S., 2009. When less is more: how fewer diagnostic criteria can indicate greater severity. *Psychol. Assess.* 21 (3), 285–293. <https://doi.org/10.1037/a0016698>.
- Cordes, D., Haughton, V., Carew, J.D., Arfanakis, K., Maravilla, K., 2002. Hierarchical clustering to measure connectivity in fMRI resting-state data. *Magn. Reson. Imaging* 20, 305–317. [https://doi.org/10.1016/S0730-725X\(02\)00503-9](https://doi.org/10.1016/S0730-725X(02)00503-9).
- Curtis, K., Viswanath, H., Velasquez, K.M., Mollesse, D.L., Harding, M.J., Aramayo, E., Baldwin, P.R., Ambrosi, E., Madan, A., Patriquin, M., Frueh, B.C., Fowler, J.C., Kosten, T.R., Nielsen, D.A., Salas, R., 2017. Increased habenular connectivity in opioid users is associated with an α5 subunit nicotinic receptor genetic variant. *Am. J. Addict.* 26 (7), 751–759. <https://doi.org/10.1111/ajad.12607>.
- Denier, N., Schmidt, A., Gerber, H., Vogel, M., Huber, C.G., Lang, U.E., Riecher-Rossler, A., Wiesbeck, G.A., Radue, E.-W., Walter, M., Borgwardt, S., 2015. Abnormal functional integration of thalamic low frequency oscillation in the BOLD signal after acute heroin treatment. *Hum. Brain Mapp.* 36 (12), 5287–5300. <https://doi.org/10.1002/hbm.23011>.
- Detre, J.A., Wang, J., 2002. Technical aspects and utility of fMRI using BOLD and ASL. *Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol.* 113 (5), 621–634. [https://doi.org/10.1016/S1388-2457\(02\)00038-x](https://doi.org/10.1016/S1388-2457(02)00038-x).
- Duff, E.P., Trachtenberg, A.J., Mackay, C.E., Howard, M.A., Wilson, F., Smith, S.M., Woolrich, M.W., 2012. Task-driven ICA feature generation for accurate and interpretable prediction using fMRI. *NeuroImage* 60 (1), 189–203. <https://doi.org/10.1016/j.neuroimage.2011.12.053>.
- Dugré, J.R., Orban, P., Potvin, S., 2023. Disrupted functional connectivity of the brain reward system in substance use problems: a meta-analysis of functional neuroimaging studies. *Addict. Biol.* 28 (1), e13257. <https://doi.org/10.1111/adb.13257>.
- Dunlop, K., Hanlon, C.A., Downar, J., 2017. Noninvasive brain stimulation treatments for addiction and major depression. *Ann. N. Y. Acad. Sci.* 1394 (1), 31–54. <https://doi.org/10.1111/nyas.12985>.
- Eickhoff, S.B., Yeo, B.T.T., Genon, S., 2018. Imaging-based parcellations of the human brain. *Nat. Rev. Neurosci.* 19, 672–686. <https://doi.org/10.1038/s41583-018-0071-7>.
- Everitt, B.J., Robbins, T.W., 2016. Drug addiction: updating actions to habits to compulsions ten years on. *Annu. Rev. Psychol.* 67 (1), 23–50. <https://doi.org/10.1146/annurev-psych-122414-033457>.
- Farahani, F.V., Karwowski, W., Lighthall, N.R., 2019. Application of graph theory for identifying connectivity patterns in human brain networks: A systematic review. *Front. Neurosci.* 13.
- Fareed, A., Kim, J., Ketchen, B., Kwak, W.J., Wang, D., Shongo-Hiang, H., Drexler, K., 2017. Effect of heroin use on changes of brain functions as measured by functional magnetic resonance imaging, a systematic review. *J. Addict. Dis.* 36 (2), 105–116. <https://doi.org/10.1080/10550887.2017.1280898>.
- Fingelkurts, A.A., Fingelkurts, A.A., Kähkönen, S., 2005. Functional connectivity in the brain—is it an elusive concept? *Neurosci. Biobehav. Rev.* 28 (8), 827–836. <https://doi.org/10.1016/j.neubiorev.2004.10.009>.
- Florence, C., Luo, F., Rice, K., 2021. The economic burden of opioid use disorder and fatal opioid overdose in the United States, 2017. *Drug Alcohol Depend.* 218, 108350. <https://doi.org/10.1016/j.drugalcdep.2020.108350>.
- Friston, K.J., Buechel, C., Fink, G.R., Morris, J., Rolls, E., Dolan, R.J., 1997. Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage* 6, 218–229. <https://doi.org/10.1006/nimg.1997.0291>.
- Friston, K.J., Harrison, L., Penny, W., 2003. Dynamic causal modelling. *NeuroImage* 19, 1273–1302. [https://doi.org/10.1016/S1053-8119\(03\)00202-7](https://doi.org/10.1016/S1053-8119(03)00202-7).
- Ge, J., Yang, G., Han, M., Zhou, S., Men, W., Qin, L., Lyu, B., Li, H., Wang, H., Rao, H., Cui, Z., Liu, H., Zuo, X.-N., Gao, J.-H., 2023. Increasing diversity in connectomics with the Chinese Human Connectome Project. *Nat. Neurosci.* 26 (1), 1. <https://doi.org/10.1038/s41593-022-01215-1>.
- Goebel, R., Roebroeck, A., Kim, D.-S., Formisano, E., 2003. Investigating directed cortical interactions in time-resolved fMRI data using vector autoregressive modeling and Granger causality mapping. *Magn. Reson. Imaging* 21, 1251–1261. <https://doi.org/10.1016/j.mri.2003.08.026>.
- Golay, X., Kollias, S., Stoll, G., Meier, D., Valavanis, A., Boesiger, P., 1998. A new correlation-based fuzzy logic clustering algorithm for FMRI. *Magn. Reson. Med.* 40, 249–260. <https://doi.org/10.1002/mrm.1910400211>.
- Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V., 2003. Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proc. Nat. Acad. Sci.* 100, 253–258. <https://doi.org/10.1073/pnas.0135058100>.
- Grossman, N., Bono, D., Dedic, N., Kodandaramaiah, S.B., Rudenko, A., Suk, H.-J., Cassara, A.M., Neufeld, E., Kuster, N., Tsai, L.-H., others, 2017. Noninvasive deep brain stimulation via temporally interfering electric fields. *Cell* 169 (6), 1029–1041.
- Guerra, A., López-Alonso, V., Cheeran, B., Suppa, A., 2020. Solutions for managing variability in non-invasive brain stimulation studies. *Neurosci. Lett.* 719, 133332. <https://doi.org/10.1016/j.neulet.2017.12.060>.

- Han, S., Northoff, G., 2008. Culture-sensitive neural substrates of human cognition: a transcultural neuroimaging approach. *Nat. Rev. Neurosci.* 9 (8), 8. <https://doi.org/10.1038/nrn2456>.
- Hasin, D.S., O'Brien, C.P., Auriacombe, M., Borges, G., Bucholz, K., Budney, A., Compton, W.M., Crowley, T., Ling, W., Petry, N.M., Schuckit, M., Grant, B.F., 2013. DSM-5 criteria for substance use disorders: recommendations and rationale. *Am. J. Psychiatry* 170 (8), 834–851. <https://doi.org/10.1176/appi.ajp.2013.12060782>.
- Hayes, A., Herlinger, K., Paterson, L., Lingford-Hughes, A., 2020. The neurobiology of substance use and addiction: evidence from neuroimaging and relevance to treatment. *BJPsych Adv.* 26 (6), 367–378. <https://doi.org/10.1192/bja.2020.68>.
- Herlinger, K., Lingford-Hughes, A., 2022. Opioid use disorder and the brain: a clinical perspective. *Addiction* 117 (2), 495–505. <https://doi.org/10.1111/add.15636>.
- Horien, C., Greene, A.S., Shen, X., Fortes, D., Brennan-Wydra, E., Banarjee, C., Foster, R., Donthireddy, V., Butler, M., Powell, K., Vernetti, A., Mandino, F., O'Connor, D., Lake, E.M.R., McPartland, J.C., Volkmar, F.R., Chun, M., Chawarska, K., Rosenberg, M.D., Constable, R.T., 2023. A generalizable connectome-based marker of in-scan sustained attention in neurodiverse youth. *Cereb. Cortex* 33 (10), 6320–6334. <https://doi.org/10.1093/cercor/bhac506>.
- Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., Sanislow, C., Wang, P., 2010. Research Domain Criteria (RDoC): toward a new classification framework for research on mental disorders. *Am. J. Psychiatry* 167 (7), 748–751. <https://doi.org/10.1176/appi.ajp.2010.09091379>.
- Jin, L., Yuan, M., Zhang, W., Su, H., Wang, F., Zhu, J., Liu, T., Wei, Y., Li, Y., Bai, Q., Wang, W., Wei, L., Li, Q., 2022. Repetitive transcranial magnetic stimulation modulates coupling among large-scale brain networks in heroin-dependent individuals: a randomized resting-state functional magnetic resonance imaging study. *Addict. Biol.* 27 (2), e13121. <https://doi.org/10.1111/adb.13121>.
- Jin, L., Yuan, M., Zhang, W., Wang, L., Chen, J., Wang, F., Zhu, J., Liu, T., Wei, Y., Li, Y., Wang, W., Li, Q., Wei, L., 2023. Default mode network mechanisms of repeated transcranial magnetic stimulation in heroin addiction. *Brain Imaging Behav.* 17 (1), 54–65. <https://doi.org/10.1007/s11682-022-00741-7>.
- Johnson, P., Fitzgerald, T., Salganicoff, A., Wood, S., Goldstein, J., 2014. Sex-Specific Medical Research: Why Women's Health Can't Wait. Brigham and Women's Hospital.
- Kas, M.J.H., Hyman, S., Williams, L.M., Hidalgo-Mazzei, D., Huys, Q.J.M., Hotopf, M., Cuthbert, B., Lewis, C.M., De Picker, L.J., Lalouis, P.A., Etkin, A., Modinos, G., Marston, H.M., 2025. Towards a consensus roadmap for a new diagnostic framework for mental disorders. *Eur. Neuropsychopharmacol.* 90, 16–27. <https://doi.org/10.1016/j.euroneuro.2024.08.515>.
- Killingsworth, M.A., Gilbert, D.T., 2010. A wandering mind is an unhappy mind. *Science* 330 (6006), 932. <https://doi.org/10.1126/science.1192439>.
- Kitayama, S., Salvador, C.E., 2017. Culture embraced: going beyond the nature-nurture dichotomy. *Perspect. Psychol. Sci.* 12 (5), 841–854. <https://doi.org/10.1177/1745691617707317>.
- Kong, R., Li, J., Orban, C., Sabuncu, M.R., Liu, H., Schaefer, A., Sun, N., Zuo, X.-N., Holmes, A.J., Eickhoff, S.B., Yeo, B.T.T., 2019. Spatial topography of individual-specific cortical networks predicts human cognition, personality, and emotion. *Cereb. Cortex* 29 (6), 2533–2551. <https://doi.org/10.1093/cercor/bhy123>.
- Kong, R., Yang, Q., Gordon, E., Xue, A., Yan, X., Orban, C., Zuo, X.-N., Spreng, N., Ge, T., Holmes, A., Eickhoff, S., Yeo, B.T.T., 2021. Individual-specific areal-level parcellations improve functional connectivity prediction of behavior. *Cereb. Cortex* 31 (10), 4477–4500. <https://doi.org/10.1093/cercor/bhab101>.
- Koob, G.F., 2006. The neurobiology of addiction: a neuroadaptational view relevant for diagnosis. *Addiction* 101 (s1), 23–30. <https://doi.org/10.1111/j.1360-0443.2006.01586.x>.
- Koob, G.F., 2009. Dynamics of neuronal circuits in addiction: reward, antireward, and emotional memory. *Pharmacopsychiatry* 42 (S 1), S32–S41. <https://doi.org/10.1055/s-0029-1216356>.
- Koob, G.F., 2021. Drug addiction: hyperkatifeia/negative reinforcement as a framework for medications development. *Pharmacol. Rev.* 73 (1), 163–201. <https://doi.org/10.1124/pharmrev.120.00083>.
- Koob, G.F., Volkow, N.D., 2010. Neurocircuitry of addiction. *Neuropsychopharmacology* 35 (1), 1. <https://doi.org/10.1038/npp.2009.110>.
- Kozak, K., Lucatch, A.M., Lowe, D.J.E., Balodis, I.M., MacKillop, J., George, T.P., 2019. The neurobiology of impulsivity and substance use disorders: implications for treatment. *Ann. N. Y. Acad. Sci.* 1451 (1), 71–91. <https://doi.org/10.1111/nyas.13977>.
- Kriegeskorte, N., Simmons, W.K., Bellgowan, P.S.F., Baker, C.I., 2009. Circular analysis in systems neuroscience: the dangers of double dipping. *Article 5. Nat. Neurosci.* 12 (5). <https://doi.org/10.1038/nn.2303>.
- Kurtin, D.L., Giunchiglia, V., Vohryzek, J., Cabral, J., Skeldon, A.C., Violante, I.R., 2023. Moving from phenomenological to predictive modelling: progress and pitfalls of modelling brain stimulation in-silico. *NeuroImage* 272, 120042. <https://doi.org/10.1016/j.neuroimage.2023.120042>.
- Kwak, L.E., Momenan, R., Litten, R.Z., Koob, G.F., Goldman, D., 2016. Addictions neuroclinical assessment: a neuroscience-based framework for addictive disorders. *Biol. Psychiatry* 80 (3), 179–189. <https://doi.org/10.1016/j.biopsych.2015.10.024>.
- Kwong, K.K., Belliveau, J.W., Chesler, D.A., Goldberg, I.E., Weisskoff, R.M., Poncelet, B. P., Kennedy, D.N., Hoppel, B.E., Cohen, M.S., Turner, R., 1992. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc. Nat. Acad. Sci.* 89, 5675–5679. <https://doi.org/10.1073/pnas.89.12.5675>.
- Lane, S.P., Sher, K.J., 2015. Limits of current approaches to diagnosis severity based on criterion counts: an example with DSM-5 alcohol use disorder. *Clin. Psychol. Sci.* 3 (6), 819–835. <https://doi.org/10.1177/2167702614553026>.
- Laumann, T.O., Gordon, E.M., Adeyemo, B., Snyder, A.Z., Joo, S.J., Chen, M.-Y., Gilmore, A.W., McDermott, K.B., Nelson, S.M., Dosenbach, N.U.F., Schlaggar, B.L., Mumford, J.A., Poldrack, R.A., Petersen, S.E., 2015. Functional system and areal organization of a highly sampled individual. *Human Brain. Neuron* 87, 657–670. <https://doi.org/10.1016/j.neuron.2015.06.037>.
- Lee, T.M.C., Zhou, W., Luo, X., Yuen, K.S.L., Ruan, X., Weng, X., 2005. Neural activity associated with cognitive regulation in heroin users: a fMRI study. *Neurosci. Lett.* 382 (3), 211–216. <https://doi.org/10.1016/j.neulet.2005.03.053>.
- Li, L.M., Uehara, K., Hanakawa, T., 2015. The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. *Front. Cell. Neurosci.* 9, 181.
- Li, K., Guo, L., Nie, J., Li, G., Liu, T., 2009. Review of methods for functional brain connectivity detection using fMRI. *Comput. Med. Imaging Graph.* 33, 131–139. <https://doi.org/10.1016/j.compmedimag.2008.10.011>.
- Li, Q., Liu, J., Wang, W., Wang, Y., Li, W., Chen, J., Zhu, J., Yan, X., Li, Y., Li, Z., Ye, J., Wang, W., 2018. Disrupted coupling of large-scale networks is associated with relapse behaviour in heroin-dependent men. *J. Psychiatry Neurosci.* 43 (1), 48–57. <https://doi.org/10.1503/jpn.170011>.
- Li, Q., Yang, W., Wang, Y., Huang, Y., Li, W., Zhu, J., Zhang, Y., Zhao, L., Qin, W., Yuan, K., von Deneen, K.M., Wang, W., Tian, J., 2013. Abnormal function of the posterior cingulate cortex in heroin addicted users during resting-state and drug-cue stimulation task. *Chin. Med. J.* 126 (4), 734. <https://doi.org/10.3760/cma.j.issn.0366-6999.20120960>.
- Li, X., Song, G., Yu, J., Ai, S., Ji, Q., Peng, Y., Zhu, X., Liu, J., 2021. Effectiveness and safety of repetitive transcranial magnetic stimulation for the treatment of morphine dependence. *Medicine* 100 (14), e25208. <https://doi.org/10.1097/MD.00000000000025208>.
- Liu, J., Qin, W., Yuan, K., Li, J., Wang, W., Li, Q., Wang, Y., Sun, J., Deneen, K.M. von, Liu, Y., Tian, J., 2011. Interaction between dysfunctional connectivity at rest and heroin cues-induced brain responses in male abstinent heroin-dependent individuals. *PLoS One* 6 (10), e23098. <https://doi.org/10.1371/journal.pone.0023098>.
- Liu, X., Zhao, X., Liu, T., Liu, Q., Tang, L., Zhang, H., Luo, W., Daskalakis, Z.J., Yuan, T.-F., 2020. The effects of repetitive transcranial magnetic stimulation on cue-induced craving in male patients with heroin use disorder. *eBioMedicine* 56. <https://doi.org/10.1016/j.ebiom.2020.102809>.
- Lu, L., Yang, W., Zhang, X., Tang, F., Du, Y., Fan, L., Luo, J., Yan, C., Zhang, J., Li, J., Liu, J., von Deneen, K.M., Yu, D., Liu, J., Yuan, K., 2022. Potential brain recovery of frontostriatal circuits in heroin users after prolonged abstinence: a preliminary study. *J. Psychiatry Res.* 152, 326–334. <https://doi.org/10.1016/j.jpsychires.2022.06.036>.
- Lueptow, L.M., Shashkova, E.C., Miller, M.G., Evans, C.J., Cahill, C.M., 2020. Insights into the neurobiology of craving in opioid use disorder. *Curr. Anesthesiol. Rep.* 10 (4), 378–387. <https://doi.org/10.1007/s40140-020-00420-7>.
- Lynch, C.J., Elbau, I.G., Ng, T., Ayaz, A., Zhu, S., Wolk, D., Manfredi, N., Johnson, M., Chang, M., Chou, J., Summerville, I., Ho, C., Lueckel, M., Bukhari, H., Buchanan, D., Victoria, L.W., Solomonov, N., Goldwasser, E., Moia, S., Liston, C., 2024. Frontostriatal salience network expansion in individuals in depression. *Nature* 633 (8030), 624–633. <https://doi.org/10.1038/s41586-024-07805-2>.
- Ma, X., Qiu, Y., Tian, J., Wang, J., Li, S., Zhan, W., Wang, T., Zeng, S., Jiang, G., Xu, Y., 2015. Aberrant default-mode functional and structural connectivity in heroin-dependent individuals. *PLoS One* 10 (4), e0120861. <https://doi.org/10.1371/journal.pone.0120861>.
- Mahoney, J.J., Haut, M.W., Carpenter, J., Ranjan, M., Thompson-Lake, D.G.Y., Marton, J. L., Zheng, W., Berry, J.H., Tirumalai, P., Mears, A., D'Haese, P., Finomore, V.S., Hodder, S.L., Rezai, A.R., 2023. Low-intensity focused ultrasound targeting the nucleus accumbens as a potential treatment for substance use disorder: safety and feasibility clinical trial. *Front. Psychiatry* 14. <https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1211566>.
- Mahoney, J.J., Thompson-Lake, D.G.Y., Ranjan, M., Marton, J.L., Carpenter, J.S., Zheng, W., Berry, J.H., Farmer, D.L., D'Haese, P., Finomore, V.S., Tirumalai, P., Mears, A.S., Suffridge, J., Ames, A., Hodder, S.L., Rezai, A.R., 2023. Low-intensity focused ultrasound targeting the bilateral nucleus accumbens as a potential treatment for substance use disorder: a first-in-human report. *Biol. Psychiatry* 94 (11), e41–e43. <https://doi.org/10.1016/j.biopsych.2023.06.031>.
- Matthews, P.M., Hampshire, A., 2016. Clinical concepts emerging from fmri functional connectomics. *Neuron* 91 (3), 511–528. <https://doi.org/10.1016/j.neuron.2016.07.031>.
- McKee, M., Dunnell, K., Anderson, M., Brayne, C., Charlesworth, A., Johnston-Webber, C., Knapp, M., McGuire, A., Newton, J.N., Taylor, D., Watt, R.G., 2021. The changing health needs of the UK population. *Lancet* 397 (10288), 1979–1991. [https://doi.org/10.1016/S0140-6736\(21\)00229-4](https://doi.org/10.1016/S0140-6736(21)00229-4).
- Medaglia, J.D., Lynall, M.-E., Bassett, D.S., 2015. Cognitive network neuroscience. *J. Cogn. Neurosci.* 27 (8), 1471–1491. <https://doi.org/10.1162/jocn.2015.00810>.
- Mehta, D.D., Praecht, A., Ward, H.B., Sanches, M., Sorkhou, M., Tang, V.M., Steele, V.R., Hanlon, C.A., George, T.P., 2024. A systematic review and meta-analysis of neuromodulation therapies for substance use disorders. *Neuropsychopharmacology* 49 (4), 4. <https://doi.org/10.1038/s41386-023-01776-0>.
- Menardi, A., Ozdemir, R.A., Momi, D., Tadayan, E., Boucher, P., Vallesi, A., Pascual-Leone, A., Shafi, M.M., santarnecchi, E., 2022. Effect of group-based vs individualized stimulation site selection on reliability of network-targeted TMS. *NeuroImage* 264, 119714. <https://doi.org/10.1016/j.neuroimage.2022.119714>.
- Menon, V., 2011. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn. Sci.* 15 (10), 483–506. <https://doi.org/10.1016/j.tics.2011.08.003>.
- Menon, V., D'Esposito, M., 2022. The role of PFC networks in cognitive control and executive function. *Neuropsychopharmacology* 47 (1), 1. <https://doi.org/10.1038/s41386-021-01152-w>.

- Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. *Brain Struct. Funct.* 214 (5), 655–667. <https://doi.org/10.1007/s00429-010-0262-0>.
- Mill, R.D., Winfield, E.C., Cole, M.W., Ray, S., 2021. Structural MRI and functional connectivity features predict current clinical status and persistence behavior in prescription opioid users. *NeuroImage Clin.* 30, 102663. <https://doi.org/10.1016/j.nicl.2021.102663>.
- Moeller, S.J., Paulus, M.P., 2018. Toward biomarkers of the addicted human brain: using neuroimaging to predict relapse and sustained abstinence in substance use disorder. *Prog. Neuro Psychopharmacol. Biol. Psychiatry* 80, 143–154. <https://doi.org/10.1016/j.pnpbp.2017.03.003>.
- Moningka, H., Lichenstein, S., Yip, S.W., 2019. Current understanding of the neurobiology of opioid use disorder: an overview. *Curr. Behav. Neurosci. Rep.* 6 (1), 1–11. <https://doi.org/10.1007/s40473-019-0170-4>.
- Nakamura-Palacios, E.M., Ronchete, C.F., Felipe, L.V., Ferreira, L.V.B., Anders, Q.S., de Melo Rodrigues, L.C., 2021. Transcranial direct current stimulation in substance use disorders. In: Brunoni, A.R., Nitsche, M.A., Loo, C.K. (Eds.), *Transcranial Direct Current Stimulation in Neuropsychiatric Disorders: Clinical Principles and Management*. Springer International Publishing, pp. 533–564. https://doi.org/10.1007/978-3-030-76136-3_27.
- National Institute for Health Care and Excellence (NICE). (2007, January 24). 7 Related NICE guidance, Methadone and buprenorphine for the management of opioid dependence, Guidance, NICE. NICE. (<https://www.nice.org.uk/guidance/ta114/chapter/7-Related-NICE-guidance>).
- Nicolas, C., Zlebnik, N.E., Farokhnia, M., Leggio, L., Ikemoto, S., Shaham, Y., 2022. Sex differences in opioid and psychostimulant craving and relapse: a critical review. *Pharmacol. Rev.* 74 (1), 119–140. <https://doi.org/10.1124/pharmrev.121.000367>.
- O'Reilly, J.X., Woolrich, M.W., Behrens, T.E.J., Smith, S.M., Johansen-Berg, H., 2012. Tools of the trade: Psychophysiological interactions and functional connectivity. *Soc. Cogn. Affect. Neurosci.* 7, 604–609. <https://doi.org/10.1093/scan/nss055>.
- Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372, n71. <https://doi.org/10.1136/bmj.n71>.
- Pandria, N., Kovatsi, L., Vivas, A.B., Bamidis, P.D., 2018. Resting-state abnormalities in heroin-dependent individuals. *Neuroscience* 378, 113–145. <https://doi.org/10.1016/j.neuroscience.2016.11.018>.
- Peters, S.K., Dunlop, K., Downar, J., 2016. Cortico-striatal-thalamic loop circuits of the salience network: a central pathway in psychiatric disease and treatment. *Front. Syst. Neurosci.* 10 <https://www.frontiersin.org/articles/10.3389/fnsys.2016.00104>.
- Polania, R., Nitsche, M.A., Ruff, C.C., 2018. Studying and modifying brain function with non-invasive brain stimulation. *Nat. Neurosci.* 21 (2), 174–187.
- Ray, D., Bezmaternykh, D., Mel'nikov, M., Friston, K.J., Das, M., 2021. Altered effective connectivity in sensorimotor cortices is a signature of severity and clinical course in depression. *Proc. Natl. Acad. Sci.* 118, e2105730118. <https://doi.org/10.1073/pnas.2105730118>.
- Rezapour, T., Rafei, P., Baldacchino, A., Conrod, P.J., Dom, G., Fishbein, D.H., Kazemi, A., Hendriks, P., Newton, N., Riggs, N.R., Squeglia, L.M., Teesson, M., Vassileva, J., Verdejo-Garcia, A., Ekhtiari, H., 2024. Neuroscience-informed classification of prevention interventions in substance use disorders: an RDoC-based approach. *Neurosci. Biobehav. Rev.* 159, 105578. <https://doi.org/10.1016/j.neubiorev.2024.105578>.
- Rogers, B.P., Morgan, V.L., Newton, A.T., Gore, J.C., 2007. Assessing functional connectivity in the human brain by fMRI. *Magn. Reson. Imaging* 25, 1347–1357. <https://doi.org/10.1016/j.mri.2007.03.007>.
- Rolls, E.T., Deco, G., Huang, C.-C., Feng, J., 2022. The effective connectivity of the human hippocampal memory system. *Cerebral Cortex* 32, 3706–3725. <https://doi.org/10.1093/cercor/bhab442>.
- Rosvall, M., Bergstrom, C.T., 2008. Maps of random walks on complex networks reveal community structure. *Proc. Natl. Acad. Sci. USA* 105 (4), 1118–1123. <https://doi.org/10.1073/pnas.0706851105>.
- Sahlem, G.L., Breedlove, J., Taylor, J.J., Badran, B.A., Lauer, A., George, M.S., Brady, K.T., Borckardt, J.J., Back, S.E., Hanlon, C.A., 2017. Dorsolateral prefrontal cortex transcranial magnetic stimulation as a tool to decrease pain and craving in opiate dependent individuals: a pilot study of feasibility and effect size. *Brain Stimul.* Basic Transl. Clin. Res. Neuromodul. 10 (2), 482. <https://doi.org/10.1016/j.brs.2017.01.412>.
- Saraiya, T.C., Jarnecke, A.M., Jones, J., Brown, D.G., Brady, K.T., Back, S.E., 2021. Laboratory-induced stress and craving predict opioid use during follow-up among individuals with prescription opioid use disorder. *Drug Alcohol Depend.* 225, 108755. <https://doi.org/10.1016/j.drugalcdep.2021.108755>.
- Schaefer, A., Kong, R., Gordon, E.M., Laumann, T.O., Zuo, X.-N., Holmes, A.J., Eickhoff, S.B., Yeo, B.T.T., 2018. Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity MRI. *Cereb. Cortex* 28 (9), 3095–3114. <https://doi.org/10.1093/cercor/bhx179>.
- Schmidt, A., Denier, N., Magon, S., Radue, E.-W., Huber, C.G., Riecher-Rössler, A., Wiesbeck, G.A., Lang, U.E., Borgwardt, S., Walter, M., 2015. Increased functional connectivity in the resting-state basal ganglia network after acute heroin substitution. *Transl. Psychiatry* 5 (3), 3. <https://doi.org/10.1038/tp.2015.28>.
- Schmidt, A., Walter, M., Gerber, H., Seifritz, E., Brenneisen, R., Wiesbeck, G.A., Riecher-Rössler, A., Lang, U.E., Borgwardt, S., 2015. Normalizing effect of heroin maintenance treatment on stress-induced brain connectivity. *Brain* 138 (1), 217–228. <https://doi.org/10.1093/brain/awu326>.
- Shen, K., Welton, T., Lyon, M., McCorkindale, A.N., Sutherland, G.T., Burnham, S., Fripp, J., Martins, R., Grieve, S.M., 2020. Structural core of the executive control network: a high angular resolution diffusion MRI study. *Hum. Brain Mapp.* 41 (5), 1226–1236. <https://doi.org/10.1002/hbm.24870>.
- Seghier, M.L., 2018. Clustering of fMRI data: The elusive optimal number of clusters. *PeerJ* 6, e5416. <https://doi.org/10.7717/peerj.5416>.
- Shen, Y., Cao, X., Shan, C., Dai, W., Yuan, T.-F., 2017. Heroin addiction impairs human cortical plasticity. *Biol. Psychiatry* 81 (7), e49–e50. <https://doi.org/10.1016/j.biopsych.2016.06.013>.
- Shen, Y., Cao, X., Tan, T., Shan, C., Wang, Y., Pan, J., He, H., Yuan, T.-F., 2016. 10-Hz repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex reduces heroin cue craving in long-term addicts. *Biol. Psychiatry* 80 (3), e13–e14. <https://doi.org/10.1016/j.biopsych.2016.02.006>.
- Smith, K., Lacadie, C.M., Miliwojovic, V., Fogelman, N., Sinha, R., 2023. Sex differences in neural responses to stress and drug cues predicts future drug use in individuals with substance use disorder. *Drug Alcohol Depend.* 244, 109794. <https://doi.org/10.1016/j.drugalcdep.2023.109794>.
- Smith, S.M., Miller, K.L., Salimi-Khorshidi, G., Webster, M., Beckmann, C.F., Nichols, T.E., Ramsey, J.D., Woolrich, M.W., 2011. Network modelling methods for FMRI. *NeuroImage* 54, 875–891. <https://doi.org/10.1016/j.neuroimage.2010.08.063>.
- Soreq, E., Leech, R., Hampshire, A., 2019. Dynamic network coding of working-memory domains and working-memory processes. *Nat. Commun.* 10 (1), 1–14.
- Spreng, R.N., Andrews-Hanna, J.R., 2015. The default network and social cognition. In: Toga, A.W. (Ed.), *Brain Mapping*. Academic Press, pp. 165–169. <https://doi.org/10.1016/B978-0-12-397025-1.00173-1>.
- Sripada, C., Angstadt, M., Taxali, A., Clark, D.A., Greathouse, T., Rutherford, S., Dickens, J.R., Shedden, K., Gard, A.M., Hyde, L.W., Weigard, A., Heitzeg, M., 2021. Brain-wide functional connectivity patterns support general cognitive ability and mediate effects of socioeconomic status in youth. *Transl. Psychiatry* 11 (1), 1–8. <https://doi.org/10.1038/s41398-021-01704-0>.
- Talati, A., Hirsch, J., 2005. Functional Specialization within the Medial Frontal Gyrus for Perceptual Go/No-Go Decisions Based on “What,” “When,” and “Where” Related Information: an fMRI Study. *J. Cogn. Neurosci.* 17 (7), 981–993. <https://doi.org/10.1162/0899929054475226>.
- Tanabe, J., Regner, M., Sakai, J., Martinez, D., Gowin, J., 2019. Neuroimaging reward, craving, learning, and cognitive control in substance use disorders: review and implications for treatment. *Br. J. Radiol.* 92 (1101), 20180942. <https://doi.org/10.1259/bjr.20180942>.
- Tibke, P. (2017). Drug Dependence Treatment in China: a Policy analysis. IDPC. (<https://idpc.net/publications/2017/02/drug-dependence-treatment-in-china-a-policy-analysis/>).
- Tiffany, S.T., Wray, J.M., 2012. The clinical significance of drug craving. *Ann. N. Y. Acad. Sci.* 1248 (1), 1–17. <https://doi.org/10.1111/j.1749-6632.2011.06298.x>.
- Tolomeo, S., Baldacchino, A., Volkow, N.D., Steele, J.D., 2022. Protracted abstinence in males with an opioid use disorder: partial recovery of nucleus accumbens function. *Transl. Psychiatry* 12 (1), 1–7. <https://doi.org/10.1038/s41398-022-01813-4>.
- Toth, J., Kurtin, D.L., Brosnan, M., Arvaneh, M., 2024. Opportunities and obstacles in non-invasive brain stimulation. *Front. Hum. Neurosci.* 18. <https://doi.org/10.3389/fnhum.2024.1385427>.
- Tsai, T.-Y., Wang, T.-Y., Liu, Y.-C., Lee, P.-W., Chang, W.-H., Lu, T.-H., Tseng, H.-H., Lee, S.-Y., Chang, Y.-H., Yang, Y., Chen, P.-S., Chen, K.-C., Yang, Y.-K., Lu, R.-B., 2021. Add-on repetitive transcranial magnetic stimulation in patients with opioid use disorder undergoing methadone maintenance therapy. *Am. J. Drug Alcohol Abus.* 47 (3), 330–343. <https://doi.org/10.1080/00952990.2020.1849247>.
- Tsui, J.I., Anderson, B.J., Strong, D.R., Stein, M.D., 2014. Craving predicts opioid use in opioid-dependent patients initiating buprenorphine treatment: a longitudinal study. *Am. J. Drug Alcohol Abus.* 40 (2), 163–169. <https://doi.org/10.3109/00952990.2013.848875>.
- Tzschentke, T.M., 2000. The medial prefrontal cortex as a part of the brain reward system. *Amino Acids* 19 (1), 211–219. <https://doi.org/10.1007/s007260070051>.
- Uddin, L.Q., Yeo, B.T.T., Spreng, R.N., 2019. Towards a universal taxonomy of macro-scale functional human brain networks. *Brain Topogr.* 32 (6), 926–942. <https://doi.org/10.1007/s10548-019-00744-6>.
- Uhl, G.R., Koob, G.F., Cable, J., 2019. The neurobiology of addiction. *Ann. N. Y. Acad. Sci.* 1451 (1), 5–28. <https://doi.org/10.1111/nyas.13989>.
- Upadhyay, J., Maleki, N., Potter, J., Elman, I., Rudrauf, D., Knudsen, J., Wallin, D., Pendse, G., McDonald, L., Griffin, M., Anderson, J., Nutile, L., Renshaw, P., Weiss, R., Becerra, L., Borsook, D., 2010. Alterations in brain structure and functional connectivity in prescription opioid-dependent patients. *Brain* 133 (7), 2098–2114. <https://doi.org/10.1093/brain/awq138>.
- van Holstein, M., Floresco, S.B., 2020. Dissociable roles for the ventral and dorsal medial prefrontal cortex in cue-guided risk/reward decision making. *Neuropsychopharmacology* 45 (4), 4. <https://doi.org/10.1038/s41386-019-0557-7>.
- Vaudano, A.E., Laufs, H., Kiebel, S.J., Carmichael, D.W., Hamandi, K., Guye, M., Thornton, R., Rodionov, R., Friston, K.J., Duncan, J.S., Lemieux, L., 2009. Causal Hierarchy within the Thalamo-Cortical Network in Spike and Wave Discharges. *PLOS ONE* 4, e6475. <https://doi.org/10.1371/journal.pone.0006475>.
- Violante, I.R., Alania, K., Cassarà, A.M., Neufeld, E., Acerbo, E., Carron, R., Williamson, A., Kurtin, D.L., Rhodes, E., Hampshire, A., Kuster, N., Boyden, E.S., Pascual-Leone, A., Grossman, N., 2023. Non-invasive temporal interference electrical stimulation of the human hippocampus. *Nat. Neurosci.* <https://doi.org/10.1038/s41593-023-01456-8>.
- Wang, D., Buckner, R.L., Fox, M.D., Holt, D.J., Holmes, A.J., Stoecklein, S., Langs, G., Pan, R., Qian, T., Li, K., Baker, J.T., Stufflebeam, S.M., Wang, K., Wang, X., Hong, B., Liu, H., 2015. Parcellating cortical functional networks in individuals. *Nat. Neurosci.* 18, 1853–1860. <https://doi.org/10.1038/nn.4164>.
- Wang, L., Hu, F., Wang, W., Li, Q., Li, Y., Zhu, J., Qin, Y., Shi, H., Li, W., Wang, Y., 2021. Altered brain intrinsic functional hubs and connectivity associated with relapse risk

- in heroin dependents undergoing methadone maintenance treatment: a resting-state fMRI study. *Drug Alcohol Depend.* 219, 108503. <https://doi.org/10.1016/j.drugalcdep.2020.108503>.
- Ward, H.B., Mosquera, M.J., Suzuki, J., Mariano, T.Y., 2020. A Systematic review of noninvasive brain stimulation for opioid use disorder. *Neuromodulation: Technol. Neural Interface* 23 (3), 301–311. <https://doi.org/10.1111/ner.13108>.
- Wei, X., Chen, J., Zhu, J., Li, Q., Li, W., Wang, W., 2021. Functional connectivity of posterior cingulate gyrus in heroin dependents treated by methadone maintenance and protracted abstinence measures: an event-related fMRI study. *Brain Imaging Behav.* 15 (5), 2472–2480. <https://doi.org/10.1007/s11682-020-00447-8>.
- Weis, S., Patil, K.R., Hoffstaedter, F., Nostro, A., Yeo, B.T.T., Eickhoff, S.B., 2020. Sex classification by resting state brain connectivity. *Cereb. Cortex* 30 (2), 824–835. <https://doi.org/10.1093/cercor/bhz129>.
- Wig, G.S., Schlaggar, B.L., Petersen, S.E., 2011. Concepts and principles in the analysis of brain networks. *Ann. New York Acad. Sci.* 1224, 126–146. <https://doi.org/10.1111/j.1749-6632.2010.05947.x>.
- Wilcox, C.E., Abbott, C.C., Calhoun, V.D., 2019. Alterations in resting-state functional connectivity in substance use disorders and treatment implications. *Prog. Neuro Psychopharmacol. Biol. Psychiatry* 91, 79–93. <https://doi.org/10.1016/j.pnpbp.2018.06.011>.
- Worsley, K.J., Chen, J.-I., Lerch, J., Evans, A.C., 2005. Comparing functional connectivity via thresholding correlations and singular value decomposition. *Philos. Trans. R. Soc. B, Biol. Sci.* 360, 913–920. <https://doi.org/10.1098/rstb.2005.1637>.
- Xia, M., Wang, J., He, Y., 2013. BrainNet Viewer: a network visualization tool for human brain connectomics. *PLOS One* 8 (7), e68910.
- Xu, Y., Wang, S., Chen, L., Shao, Z., Zhang, M., Liu, S., Wen, X., Li, Y., Yang, W., Tang, F., Luo, J., Fan, L., Yan, C., Liu, J., Yuan, K., 2021. Reduced midbrain functional connectivity and recovery in abstinent heroin users. *J. Psychiatr. Res.* 144, 168–176. <https://doi.org/10.1016/j.jpsychires.2021.10.011>.
- Xue, J., Chen, J., Wang, S., Li, W., Zhu, J., Wang, F., Li, Z., Wang, W., Li, Q., 2022. Assessing brain activity in male heroin-dependent individuals under methadone maintenance treatment: a resting-state fMRI study. *Psychiatry Res. Neuroimaging* 320, 111431. <https://doi.org/10.1016/j.pscychresns.2021.111431>.
- Yang, W., Wang, S., Luo, J., Yan, C., Tang, F., Du, Y., Fan, L., Zhang, M., Zhang, J., Yuan, K., Liu, J., 2022. Longitudinal resting-state functional connectivity changes in the insular subdivisions of abstinent individuals with opioid use disorder. *Psychiatry Res.* 317, 114808. <https://doi.org/10.1016/j.pscychres.2022.114808>.
- Yaple, Z.A., Yu, R., 2020. Functional and structural brain correlates of socioeconomic status. *Cereb. Cortex* 30 (1), 181–196. <https://doi.org/10.1093/cercor/bhz080>.
- Yeo, B.T.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., Roffman, J.L., Smoller, J.W., Zöllei, L., Polimeni, J.R., Fischl, B., Liu, H., Buckner, R. L., 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J. Neurophysiol.* 106 (3), 1125–1165. <https://doi.org/10.1152/jn.00338.2011>.
- Yuan, K., Qin, W., Dong, M., Liu, J., Sun, J., Liu, P., Zhang, Y., Wang, W., Wang, Y., Li, Q., Zhao, L., von Deneen, K.M., Liu, Y., Gold, M.S., Tian, J., 2010. Gray matter deficits and resting-state abnormalities in abstinent heroin-dependent individuals. *Neurosci. Lett.* 482 (2), 101–105. <https://doi.org/10.1016/j.neulet.2010.07.005>.
- Zhang, R., Volkow, N.D., 2019. Brain default-mode network dysfunction in addiction. *NeuroImage* 200, 313–331. <https://doi.org/10.1016/j.neuroimage.2019.06.036>.
- Zhang, S., Yang, W., Li, M., Wang, S., Zhang, J., Liu, J., Yuan, K., 2022. Partial recovery of the left DLPFC-right insula circuit with reduced craving in abstinent heroin users: a longitudinal study. *Brain Imaging Behav.* 16 (6), 2647–2656. <https://doi.org/10.1007/s11682-022-00721-x>.
- Zhang, S., Yang, W., Li, M., Wen, X., Shao, Z., Li, J., Liu, J., Zhang, J., Yu, D., Liu, J., Yuan, K., 2022. Reconfigurations of dynamic functional network connectivity in large-scale brain network after prolonged abstinence in heroin users. *Curr. Neuropharmacol.* <https://doi.org/10.2174/1570159X21666221129105408>.
- Zhang, Y., Tian, J., Yuan, K., Liu, P., Zhuo, L., Qin, W., Zhao, L., Liu, J., von Deneen, K. M., Klahr, N.J., Gold, M.S., Liu, Y., 2011. Distinct resting-state brain activities in heroin-dependent individuals. *Brain Res.* 1402, 46–53. <https://doi.org/10.1016/j.brainres.2011.05.054>.