

# Unfolding the real-time neural mechanisms in addiction: Functional near-infrared spectroscopy (fNIRS) as a resourceful tool for research and clinical practice

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## ABSTRACT

Neural underpinnings of addiction have been widely investigated using traditional neuroimaging techniques and paradigms. However, certain mechanisms are still underexplored, and existing studies often do not adopt an ecological assessment. Functional near-infrared spectroscopy (fNIRS) emerges as a potential elective tool to assess real-time neural activity with high ecological validity, as well as a good spatial and temporal resolution. So far, fNIRS has been rarely used as an instrument to study the neural underpinnings of substance and behavioral dependence. Starting from the available scientific literature, we aim to present the various applications of fNIRS in the research field of addiction, leading to unprecedented advancements in research and clinical practice.

## 1. Introduction

Addiction is defined as a state in which a person is unable to self-regulate the consumption of a substance or a behavior [36,51]. In the substances use *continuum*, people with addiction represent the most extreme group. In fact, these individuals display moderate to high severity of substance use disorder (i.e., the diagnostic label in the fifth edition of the Diagnostic and Statistical Manual of Mental Health Disorders; DSM-5) [36].

Although people can develop an addiction to a multitude of both legal and illegal substances (e.g., alcohol and drugs) and behaviors (e.g., gambling, gaming, sex, exercise). Nevertheless, the inability to regulate the consumption of a specific substance/behavior is regarded as a unique manifestation of the same underlying addiction syndrome [74]. In particular, all types of addiction appear to have a dysregulation in the reward system of the brain (i.e., the mesolimbic and mesocortical pathways and the related dopamine levels) [28]. Together with the traditional biological basis, addiction has also been shown to depend on psychological and social components [35,51,58]. For instance, Zilberman et al. [87] documented higher impulsivity and neuroticism (a personality trait associated with the tendency to respond with negative emotions to threat, frustration, or loss [19,50]) across all individuals with an addiction compared to the control group. Additionally, authors

observed addiction-specific patterns of personality traits. For instance, lower traits of extraversion, agreeableness, and openness to experience were particularly frequent in participants with alcohol use disorders. Hence, the bio-psycho-social model proposed by Engel [24] is useful to frame and understand the underlying mechanisms of addiction [12,75].

In the past decades, the advent of neuroimaging techniques, mainly in terms of positron emission tomography (PET), structural magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), and electroencephalography (EEG), has provided valuable insight into the neurophysiological substrates of addiction [27,29,33,62,83]. For instance, the meta-analysis of fMRI studies by Klugah-Brown et al. [48] highlights the existence of a shared pattern of neural abnormalities across substances in people with addiction. Specifically, alterations in the dorsal striatal and frontal circuits, which are typically involved in reward and salience processing, habit creation, and executive control, are commonly observed across substances and experimental paradigms [36,48]. Despite the valuable set of evidence collected with the traditional neuroimaging techniques on the substrates of addiction, these techniques still have some drawbacks. For instance, while PET and fMRI both provide high spatial resolution to investigate brain activity, they are also expensive to use and not portable. Furthermore, both PET and fMRI require participants to stay stationary in artificial scanners and they do not provide good temporal resolution for the study

**Abbreviations:** DSM, Diagnostic and Statistical Manual of Mental Health Disorders; EEG, Electroencephalography; fMRI, Functional Magnetic Resonance Imaging; fNIRS, Functional Near-Infrared Spectroscopy; HbO, Oxygenated Hemoglobin; HbR, Deoxygenated Hemoglobin; MRI, Magnetic Resonance Imaging; PET, Positron Emission Tomography; THC,  $\Delta^9$ -Tetrahydrocannabinol.

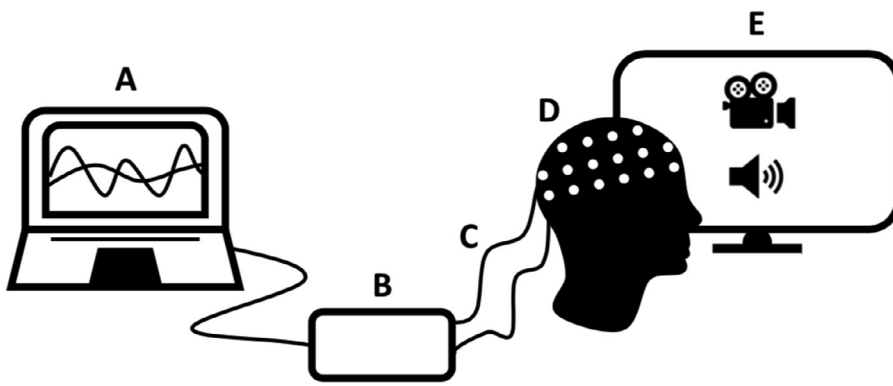
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**Fig. 1.** Schematic representation of a typical functional near-infrared spectroscopy (fNIRS) system. The main components of the system are: A) Acquisition laptop; B) fNIRS unit; C) fNIRS cables; D) fNIRS cap with optodes; E) Monitor to present stimuli (i.e. sounds, pictures, videos, etc.).

of neural activity. In addition, PET is invasive as it relies on the injection of radioactive components to measure brain activity. Conversely, EEG provides an optimal temporal resolution to investigate brain activity, is moderately portable, and also cost-effective. Nevertheless, EEG has poor spatial resolution [57,66].

Functional near-infrared spectroscopy (fNIRS) is a recently introduced neuroimaging technique. fNIRS is a non-invasive optical neuroimaging technique that estimates brain activity from variations in cerebral blood oxygenation levels in terms of oxygenated (HbO) and deoxygenated hemoglobin (HbR; see Fig. 1 for a representation of the fNIRS system). To do so, near-infrared (NIR) light (wavelength 650–950 nm) is shone from light sources to light detectors and forms a photon pathway. The NIR light in the photon pathway travels through several biological layers of the head (e.g., skin, skull, cerebrospinal fluid) to reach the light detector. This is due to the relative transparency of human skin and bones to NIR light (i.e., the NIR optical window) [45,64].

There are a number of advantages that enable fNIRS to be a valid solution to overcome some of the limitations of traditional neuroimaging methods [82]. For example, fNIRS is less sensitive to motion artifacts as compared to EEG, PET, and fMRI [9,26]. Moreover, unlike PET and fMRI, it has the advantage of being cost effective, small, and portable [46,53]. As a whole, these features have encouraged the use of fNIRS to investigate brain activity in ecological settings and during real-life social interactions [7,23,43]. For these reasons, fNIRS has been recently adopted as an elective device in hyperscanning studies, where the brain activity of two or more individuals is recorded simultaneously during social interactions [4,5,11].

## 2. Methods

The current narrative review aims to analyze the emerging contribution of fNIRS in the study of addiction from a qualitative perspective. The literature search was conducted using PubMed Central, Scopus, and Google Scholar. The string of keywords used to drive the literature search in all platforms was “fNIRS and addiction”. Only studies in which fNIRS was adopted to investigate specific components of addiction in the bio-psycho-social framework were considered for analysis.

We included original investigations published in peer-reviewed journals. All the included studies used fNIRS to investigate (i) biological, (ii) psychological, or (iii) social components of addiction. Both longitudinal and cross-sectional research, together with retrospective and prospective studies, were included. The search was limited to articles written in English to ensure the inclusion of studies representing the rigorous and standardized international scientific literature on the field [10,14]. Studies published in a different language than English, or unrelated to the topic of interest, were excluded from the discussion. As done in Cataldo et al. [13], we also excluded case reports or series, opinion papers such as editorials, letters to the editor with no data, hypotheses, meta-analyses, or reviews.

In the following sections, we provide an overview of the fNIRS-based studies on addiction under the light of the bio-psycho-social model proposed by Engel [24]. To reflect the components of the bio-psycho-social model, we have clustered the eligible contributions in the following main groups: (i) fNIRS and the biological signature of addiction; (ii) fNIRS and the psychological component of addiction; and (iii) fNIRS and the social environment of addiction. Furthermore, we have also included the section (iv) fNIRS in addiction treatment to highlight the potentially leading role of fNIRS in driving translational research on addiction. Finally, (v) we provide a short overview of the limitations that might have contributed to hindering the usage of fNIRS in addiction research.

## 3. Results

### 3.1. fNIRS and the biological signature of addiction

Several studies have recently taken advantage of the spatial properties of fNIRS to investigate the functioning of the brain in individuals with addiction. Studies have mainly focused on examining the prefrontal cortex of individuals with addiction to substances and behaviors, such as cannabis, psilocybin, tobacco, ecstasy, opiates, and gaming [34,73]. For instance, Keles et al. [47] explored the feasibility of fNIRS to assess the impact of  $\Delta$ 9-Tetrahydrocannabinol (THC), the primary psychoactive compound in cannabis, on the prefrontal cortex functioning. The rationale for the study is that the prefrontal cortex contains a large number of cannabinoid receptors CB1 to which THC binds [31]. In the experiment, fNIRS was used to assess brain activity in two time points: before and approximately two hours after THC administration. During the fNIRS assessment, participants took part in a letter *n*-back working memory task, divided into two conditions: one with low working memory load and one with high working memory load. In the condition with low working memory load, participants were asked to press a response button whenever the letter “X” appeared on the screen. In the condition with high working memory load, participants were instructed to press the button when the presented letter corresponded to the one presented two trials before. Conditions were presented in a blockwise fashion and each condition was repeated six times. In the study, after THC administration, the authors observed a significant increase in HbO concentration in the participants’ prefrontal cortex during both conditions of the working memory task. Accordingly, Gilman et al. [31] suggested that the increased brain activity in the prefrontal cortex might be a potential biomarker for cannabis intoxication. Similarly, fNIRS has proved useful to investigate prefrontal functioning in individuals using tobacco [54], ecstasy [60,71], and opiates [39,43,44]. With regards to opiate addiction, Jeong et al. [42] used machine learning to combine fNIRS and EEG information to shed light on the neuroadaptation of the prefrontal cortex during heroin abstinence. Results showed that individuals with heroin addiction demonstrated desynchronized lower alpha rhythms and decreased connectivity in prefrontal cortex networks.

**Table 1**

Table with the list of reviewed publications on functional near-infrared spectroscopy (fNIRS) and the biological signature of addiction. A brief overview of their common contribution is provided.

fNIRS and the biological signature of addiction	
Reference	Cluster summary
Cho et al. [16] Cuesta et al. [20] Keles et al. [47] Kornev et al. [49] George and Koob [30] Gilman et al. [31] Gu et al. [34] Huhn et al. [39] Jeong and Yuan [43] Jeong and Yuan [44] Jeong et al. [42] Liu et al. [54] Montgomery and Roberts [60] O'Doherty et al. [61] Qi et al. [67] Roberts et al. [71] Scholkmann et al. [73]	In this cluster of publications, researchers used fNIRS to investigate the neural underpinnings of addiction to substances and behaviors, with a focus on the prefrontal cortex function.

In the literature, the investigation of the biological basis of addiction through fNIRS was extended beyond pharmacological substances. Some preliminary studies used fNIRS to explore the underlying mechanisms of behavioral addictions (i.e., gaming behavior, internet use, and porn consumption) [20,49]. For example, Cho et al. [16] investigated the neural basis of internet gaming disorder through fNIRS while participants engaged in real-time gaming sessions. Specifically, participants were asked to play League of Legends, a popular multiplayer online battle arena game. fNIRS was used to assess neural activity while participants played one game round, which typically lasts between 20 to 50 min. For each participant, their gameplay was video recorded and evaluated in terms of positive and negative events by experienced League of Legends players. By retrieving the timestamps of the identified positive and negative game events, the authors were able to investigate changes in cerebral blood oxygenation levels with an event-related approach. The authors observed stronger neural activity in the dorsolateral prefrontal cortex during positive game events (e.g., opposing team is defeated) and weaker neural activity in the lateral orbitofrontal cortex during negative game events (e.g., participant's team is defeated) for individuals with internet gaming disorder as compared to the control group. Typically, the dorsolateral prefrontal cortex is activated by substance-related cues and its activation positively correlates with the feelings of craving [30,67]. Conversely, existing literature suggests that the activity of the lateral orbitofrontal cortex seems to be associated with unpleasant stimuli and punishment [61]. Hence, based on their results, Cho et al. [16] posited that when people with internet gaming disorder experience desired game events, they crave to engage in more internet gaming. Conversely, during negative game events, people with internet gaming disorder show less sensitivity to negative in-game experiences as compared to people without the disorder. See Table 1 for an overview of the current section.

### 3.2. fNIRS and the psychological component of addiction

In the literature on addiction, fNIRS has been used to investigate some psychological factors such as self-control, cognitive functioning, emotion regulation, and approach-avoidance reactions. These factors are known to play a role in the maintenance of substance use and addiction [2,3,6,25,26,40,55,70,84]. In particular, the fNIRS-based studies by Chen et al. [15], Colledge et al. [18], Qi et al. [67] suggested that physical exercise might be beneficial for individuals with addiction, as it seems to enhance people's self-control over the cue-induced substance cravings. For instance, in individuals with addiction

**Table 2**

Table with the list of reviewed publications on functional near-infrared spectroscopy (fNIRS) and the psychological component of addiction. A brief overview of their common contribution is provided.

fNIRS and the psychological component of addiction	
Reference	Cluster summary
Alizadehgoradel et al. [1] Asaoka et al. [2] Asaoka et al. [3] Balconi et al. [6] Chen et al. [15] Colledge et al. [18] Ernst et al. [26] Ernst et al. [25] Huhn et al. [40] Maier et al. [55] Monroe et al. [59] Qi et al. [67] Roberts and Montgomery [70] Witte et al. [84]	This cluster of publications includes articles in which fNIRS was used to investigate some of the psychological factors that are crucial for the maintenance of substance use behavior.

to methamphetamine, the exposure to substance-related cues typically elicits higher neural activity in prefrontal regions (i.e., dorsolateral prefrontal cortex and orbitofrontal cortex) and this heightened neural activity is associated with increased substance cravings. To study the beneficial role of physical exercise in addiction, Qi et al. [67] combined fNIRS with a block design behavioral paradigm (i.e., drug-cue reactivity task) and virtual reality. In particular, the experiment consisted of two sessions of a drug-cue reactivity task separated by a 10-min session of a cycling competition in a virtual reality environment and about 600 min of rest. During the drug-cue reactivity task, participants were shown 4 drug-related or neutral images in a randomized order while their neural activity was assessed with fNIRS. After a session of acute exercise in a virtual reality environment, the authors observed decreased hemodynamic responses in the dorsolateral prefrontal cortex and orbitofrontal cortex during the exposure to substance-related cues. This finding suggests that a session of physical exercise was followed by higher self-control over cue-induced cravings. Similarly, in smokers, physical exercise can reduce mood disturbances (i.e., tension-anxiety, depression, fatigue, and confusion). This is relevant as mood disturbances typically function as negative reinforcement for the smoking behavior itself [59]. As substances like methamphetamine, nicotine, or heroin are known to induce frequent relapses triggered by substance-related cues, a better understanding of the modulators of individuals' self-control and substance craving is of great translational importance [1,15,67]. See Table 2 for an overview of the current section.

### 3.3. fNIRS and the social environment in addiction

fNIRS has been used to investigate specific aspects of the individual's social life (e.g., social cognition, perceived occupational stress, communication of emotion) in typical and psychiatric populations [17,63,65,72,86]. When considering its properties, fNIRS appears as an elective tool to study the person in their social environment. Furthermore, its portability makes fNIRS an ideal device with high ecological validity as it allows recording brain activity in naturalistic settings [7]. For these reasons, fNIRS is now commonly adopted in hyperscanning studies to better understand the neural mechanisms of real-life social interactions [4,5]. For example, Azhari et al. [4] used fNIRS to assess the neural activity of two participants (i.e., a mother and their biological child) during a passive exposure to visual stimuli (i.e., one-minute video clips) in a tandem experimental session. Despite the properties of fNIRS and despite the fact that many factors associated with the individual's social world (e.g., affiliation with deviant peers, popularity, bullying) appear to contribute to the onset and maintenance of addiction [81], no

**Table 3**

Table with the list of reviewed publications on functional near-infrared spectroscopy (fNIRS) and the social environment in addiction. A brief overview of their common contribution is provided.

fNIRS and the social environment in addiction	
Reference	Cluster summary
Azhari et al. [4]	This cluster of publications examined the benefits of using fNIRS in social neuroscience. It emerged that no study has yet used fNIRS to investigate the contribution of social environment in addiction.
Azhari et al. [5]	
Bizzego et al. [7]	
Chou et al. [17]	
Pinti et al. [63]	
Pu et al. [65]	
Rojiani et al. [72]	
Whitesell et al. [81]	
Zhang et al. [86]	

study has used fNIRS to investigate the role played by social factors in addiction yet. See Table 3 for a summary of the current section.

### 3.4. fNIRS in addiction treatment

Evidence of selective functional changes in the brain of people with addiction has fostered the adoption of fNIRS as a diagnostic and prognostic biomarker of addiction severity [23,69]. In fact, fNIRS represents a valid alternative to fMRI in translational settings, given its safety, cost effectiveness, and patient-friendliness [9]. fNIRS-based studies have primarily been conducted to monitor recovery in people with addiction undergoing a phase of substance abstinence [21,41,76]. In particular, the study by Dempsey et al. [21] used fNIRS to measure brain activity in a sample of individuals with addiction to alcohol across various degrees of abstinence (i.e., abstinence duration range: from 1 month to 10 years) when exposed to alcohol-related images. In the study, the authors reported a negative association between days of substance abstinence and prefrontal reactivity to substance-related cues in people with an alcohol addiction. In these participants, a longer abstinence was associated with lower activity in the dorsolateral and dorsomedial prefrontal cortices in response to substance-related cues. Similarly, Huhn et al. [41] used fNIRS during a drug-cue reactivity paradigm to monitor relapses of opioid use in methadone-maintained patients. Results of the study showed that the activity in the left lateral prefrontal cortex elicited by substance cues was significantly associated with participants' percent opioid-negative urine screens. In particular, the neural activity in the left lateral prefrontal cortex was a strong predictor of current opioid use with a classification accuracy of 86%. A strong predictive model for opioid use was subsequently built by combining fNIRS data, baseline craving scores, and self-reported depressive symptoms. fNIRS has also been recently used for treatment purposes. For instance, in the study by Walia et al. [80], evidence on cue-reactivity was used to develop a neuroimaging-guided noninvasive brain stimulation approach to ameliorate the maladaptive learnt neural responses in people with addiction.

Finally, fNIRS has also been used in translational research to monitor the evolution of the psychological symptoms (i.e., anhedonia and demoralization) and personality traits (i.e., impulsivity) that determine the successful recovery from addiction [38,79]. For instance, Huhn et al. [38]'s study consisted of a sample of participants maintained on methadone. Participants' depressive symptoms, anhedonia, and demoralization were assessed directly after methadone dosing. Two hours after methadone dosing, participants took part in a natural reward cue reactivity task while their brain activity was assessed with fNIRS. Visual stimuli consisted of natural reward cues (i.e., highly palatable food, positive social interactions, and emotional intimacy) or emotionally neutral images. Positive reward stimuli were displayed by type in a blockwise fashion for 250 s (5 images displayed for 50 s each). Results of the study showed that participants reporting higher levels of anhedonia tend to

**Table 4**

Table with the list of reviewed publications on functional near-infrared spectroscopy (fNIRS) in addiction. A brief overview of their common contribution is provided.

fNIRS in addiction treatment	
Reference	Cluster summary
Bunce et al. [9]	This cluster of publications foster the adoption fNIRS as a diagnostic and prognostic device to evaluate substance use severity and its related psychological symptoms. Moreover, the use fNIRS for treatment purposes also emerged.
Dempsey et al. [21]	
Ehlis et al. [23]	
Huhn et al. [41]	
Huhn et al. [38]	
Rahman et al. [69]	
Stewart et al. [76]	
Veit et al. [79]	
Walia et al. [80]	

display reduced brain activity in the right prefrontal cortex when exposed to natural reward cues. Moreover, with regard to positive social cues, higher anhedonia was significantly associated with lower neural activity in the right ventromedial prefrontal cortex. Similarly, higher demoralization was significantly associated with reduced brain activity in an region including the right lateral ventromedial prefrontal cortex and the dorsolateral prefrontal cortex. See Table 4 for a summary of the cluster.

### 3.5. Limitations in the uptake of fNIRS in addiction research

Despite the growing number of fNIRS-based research, some limitations in the device and in its usage might have prevented its adoption in neuroscience and, particularly, in addiction research. For instance, fNIRS has a scarce penetration depth and thus cannot be used to measure brain activity in subcortical areas crucial for addiction research [68]. In fact, the penetration depth of fNIRS results as a compromise between spatial/depth sensitivity and signal-to-noise ratio, both of which tend to increase accordingly to the source-detector separation [64,77]. A balance between sensitivity and signal-to-noise ratio is commonly reached with the ideal source-detector separation of 30–35 mm in adults [64]. Together with its scarce penetration depth, fNIRS also poses the issue of not providing structural information of the brain for anatomical reference, making the co-registration to standard brain atlases challenging [56,68].

The adoption of fNIRS is also characterized by a technical and computational heterogeneity across research groups and across studies. For instance, different studies might adopt different fNIRS devices. These devices may vary in terms of hardware operations and overall methodology to measure cerebral blood oxygenation levels. Additionally, different studies may also adopt different design of the source–detector matrix (e.g., optodes location, source–detector distance, source–detector array density) [85]. This diversity in research practises poses a serious challenge for the interpretation, reproducibility, and cross-comparability of findings and thus marks the infancy of the technique in neuroscience [85]. For these aforementioned reasons, recent works are focusing on the definition of best practices and standardized computational approaches for fNIRS studies [8,85].

## 4. Conclusion

The current narrative review explored the emerging contributions on the use of fNIRS in addiction research and clinical practice. Thanks to its advantages over traditional neuroimaging techniques, fNIRS has shown to be a resourceful instrument to shed new light on the biological and psychological mechanisms in substance-based and behavioral addictions. In particular, scholars have focused on investigating the functioning of the prefrontal cortex, which is crucial for the top-down control in addiction [32,67]. From the literature, it also emerged that the

integration of neuroimaging and behavioral evidence has inspired the development of new fNIRS-based approaches to better predict patients' prognosis and recovery from addiction in clinical practice.

Despite the insights provided by fNIRS in the neuroscience of addiction, there is room for future lines of research. For instance, no existing study has used fNIRS to investigate the role played by social factors in clinical trajectories of substance use and addiction. In fact, fNIRS is regarded as an elective tool in social neuroscience as it allows recording of real-time social interactions with high ecological validity [22]. Taking advantage of these properties of fNIRS to investigate the social component of addiction would provide a more comprehensive understanding of the bio-psycho-social basis of the disorder. Further consideration of the clinical trajectories of addiction might also inspire fNIRS-based neurofeedback clinical interventions to ameliorate patients' maladaptive learnt neural responses [37,52,78].

#### Authors contribution

Conceptualization: AC, IC, GE; Methodology: IC; Formal Analysis: AC, IC; Investigation: AC, IC; Writing—original draft preparation: AC; Writing—review and editing: AC, IC, SF, OC, GE; Supervision: GE. All authors have read and agreed to the published version of the manuscript.

#### Declaration of Competing Interest

Authors declare that they have no conflict of interest.

#### Data availability

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

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