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Applications of Fiber Photometry in Social Behavior, Addiction, and Mood Affect Research: A Literature Review

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Fiber photometry is an exciting technique developed in the early 2000s to record neural activity in awake, behaving subjects. This technology utilizes components similar to optogenetics, such as fiber optic implants and fluorescent biosensors. Still, it offers an alternative approach to understanding neural populations and circuitry- to record rather than manipulate. Additionally, fiber photometry resembles two-photon microscopy and miniscopes as all three were originally developed to use calcium imaging. However, fiber photometry has the added benefit of recording in freely moving animals and images at deeper brain regions, respectively. With these unique characteristics, fiber photometry has caught the interest of several fields of study, including social behavior, addiction, and mood affect, each of which has adapted this technique to fit their needs. Some key adaptations include the creation of new biosensors (i.e., dopamine, serotonin, norepinephrine), transgenic animal lines (i.e., cre-lox), and complex recording paradigms (i.e., fiber photometry in tandem with optogenetics and/or chemogenetics). Fiber photometry builds upon existing electrophysiological techniques and offers a powerful method to validate previously reported results or yield novel results. To this end, this technique has transformed how researchers study the brain and its activity preceding, during, or following behavioral events.

INTRODUCTION

What is Fiber Photometry

Fiber photometry allows for the visualization of neural population activity in awake, freely moving rodents [1]. This revolutionary technique was first developed at the Ludwig Maximilian University of Munich to image calcium activity as a proxy for neural activity in newborn mice [2]. Their foundational calcium

imaging principles were then further developed by Karl Deisseroth's lab Stanford University [3]. However, fiber photometry has evolved exponentially in just a few decades, giving way to countless new applications [4-6]. This technique's undeniable impact and versatility have revolutionized studying the relationship between behavior and the brain.

In this review, we will discuss how fiber photometry compares to and can complement existing neural techniques, as well as its applications within the studies of social behavior (e.g., maternal, social interaction, aggression, and mating), addiction (e.g., substance use, withdrawal, and relapse), and mood affect (e.g., depression, anxiety, and antidepressants). These three fields are associated with the reward system and dopaminergic signaling. [7-13]Several social behaviors, including mother-pup interactions, social play, social investigation, and mating, are inherently rewarding to rodents and require the synergy of several brain regions (e.g., hypothalamus, amygdala, nucleus accumbens, ventral tegmental area, medial prefrontal cortex, periaqueductal gray) and neurochemicals (e.g., oxytocin, vasopressin, dopamine, prolactin) to coordinate efficient interactions [7, 8, 14-17]. On the other hand, substance use utilizes the reward system to reinforce drug-seeking behavior powerfully. [10, 18, 19]. To this end, repeated substance use and/or substance abuse can dysregulate the natural reward system and ultimately lead to maladaptive behaviors and abnormal responses to rewarding stimuli. [9, 11, 20]. Similarly, mood disorders like depression are associated with changes in motivation and/or stimulus salience, both of which are modulated by the reward system. [12, 13, 21, 22]. Taken together, studies that have utilized fiber photometry within social behavior, addiction, and mood affect demonstrate how this neural technique has transformed the study of neural circuitry.

METHODS

Biological Components

To image calcium ion activity, a genetically encoded calcium indicator (GECI) equipped with a fluorescent protein (i.e., green fluorescent protein [GFP] or tandem dimer tomato [tdTomato]) is incorporated into the structure of calcium receptors [23, 24]. The GECI is typically expressed using a viral microinjection in the brain region of interest. Once calcium is bound, the receptor undergoes a conformational change, allowing the encoded sensor to fluoresce [25, 26]. The resulting illumination is picked up and transmitted by the fiber optic and transformed into a trace representing the intensity of light illuminating from the brain region. Thus, the greater the light intensity, the greater the calcium activity was. A commonly used GECI is GCaMP [27]. However, biosensors developed for fiber photometry have not stopped with calcium indicators. In the past decade, dozens of sensors have been created for specific neurotransmitters, including glutamate [28], GABA [29], serotonin [30], dopamine [31-34], norepinephrine [35], and oxytocin [36], to

name a few. With the development of these fluorescent biosensors, the applications of fiber photometry have become limitless.

In addition to the development of new fluorescent biosensors, transgenic rodent lines have evolved to target specific cell types. Briefly, transgenic animals have been bred with unique and specific genetic features (i.e., knock-in or knock-out). A commonly used transgenic system for fiber photometry experiments is the Cre-Lox system [37]. This technique relies on knock-in animals expressing the enzyme cre recombinase within a specific cell or tissue type [38], and requires the encoding of loxP sites before and after the target gene(s). When the enzyme Cre recombinase is present, the two loxP sites are bound together, which can result in excision, inversion, or translocation of the encased gene(s) [39, 40]. In other words, using a Cre-Lox system allows for cell-specific control over select gene expression. By using a cre-dependent virus to express the GECI, researchers can selectively express their biosensor of choice in specific cell types.

Technical Components

Getting the right equipment is crucial when using the fiber photometry apparatus for studying brain activity. The main components can be swapped for different variations for different signaling molecules and strengths. In a common system, the process begins with the light source, typically an LED or laser, which generates light at specific wavelengths to excite fluorescent molecules in the sample. The light is then transmitted through fiber-optic patch cables, which direct it to the tissue, where a cannula holds the fiber in place for precise light delivery. The LED driver powers the fiber-coupled LEDs, ensuring consistent light output for the excitation of fluorophores. After the tissue emits fluorescence, the signal travels back through the fiber-optic cables and is captured by a high bandwidth detector, which provides high temporal resolution for accurate measurements. To minimize background interference, low-autofluorescence patch cables are used, reducing signal noise. The fluorescence is filtered by fiberoptic filter cubes, which isolate the desired wavelengths, often 405 nm and 470 nm, for detection. In general, two different wavelengths are delivered to the tissue, a control, isosbestic wavelength which corrects for motion artifacts and autofluorescence (i.e., 405 nm or 415 nm) and an excitation wavelength (i.e., 470 nm, 560 nm) which detects biosensor-specific fluorescence. An example of the fiber photometry system can be seen in figure 1 (Thorlabs).

In addition to the core components of a fiber photometry setup, there are several additional pieces of equipment that can enhance the system's functionality. Optical isolators are often used to prevent light from reflecting into the light source, which could otherwise interfere with measurements. Beam splitters are used to direct light to multiple pathways, allowing for simultaneous use of different wavelengths for excitation or the collection of emission signals. Microscopes or endoscopes can be integrated for precise imaging and light delivery in more localized or deep-brain structures. For experiments involving multiple channels of fluorescence, multiplexing equipment allows the simultaneous collection of signals from different fluorescent markers. Lock-in amplifiers may also be employed to increase signal clarity by synchronizing

with modulation frequencies, allowing for more sensitive detection of weak signals. Additionally, voltage-controlled attenuators can adjust the intensity of the light to prevent photobleaching or damage to delicate samples. Together, these tools expand the versatility and sensitivity of fiber photometry systems, making them applicable in a wider range of experimental scenarios, from neural activity monitoring to dynamic cellular imaging.

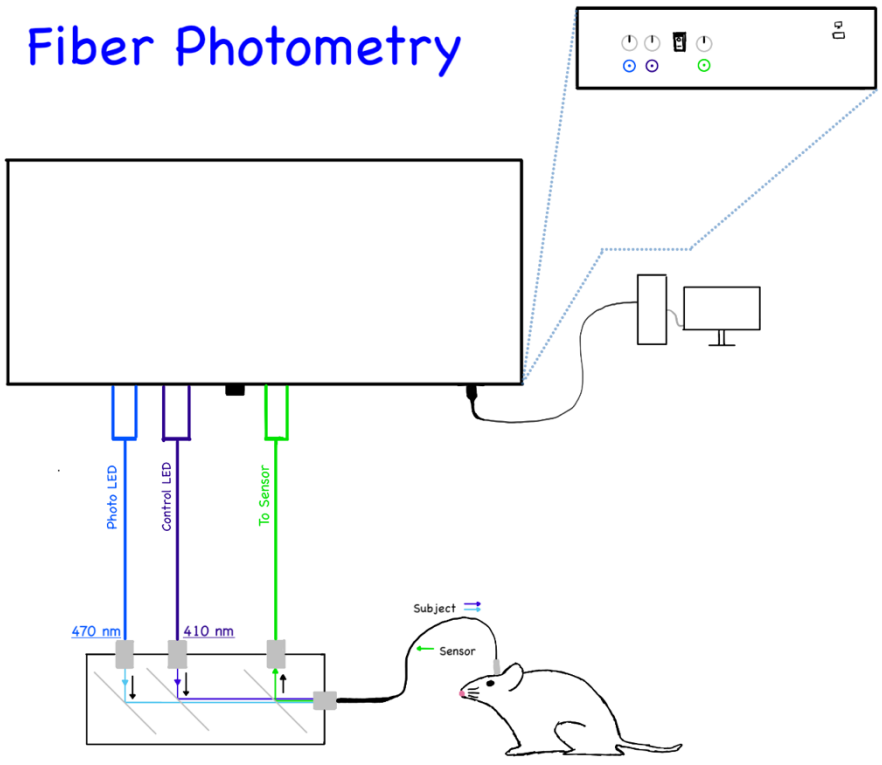

Figure 1: Fiber Photometry apparatus example diagram.

Analysis

Data analysis is a critical component of fiber photometry experiments, as it allows researchers to interpret fluorescence signals in the context of behavioral activity. Because raw signals can be influenced by factors such as motion artifacts or photobleaching, a control channel—often using an isosbestic wavelength—is used to correct for these non-neuronal fluctuations. The corrected signal is then normalized to a baseline fluorescence value, typically expressed as a change in fluorescence over baseline (ΔF/F) (Sherathiya et al., 2021). Furthermore, to normalize signal across several recording sessions and/or animals, the z-score of the ΔF/F can be taken. Accurate signal normalization requires a careful understanding of biosensor dynamics, signal alignment, and regression, which can present challenges for those new to the technique.

While most labs use custom-written scripts to analyze their fiber photometry data, we discuss a few open-source options for fiber photometry analysis that are especially helpful for labs looking to start fiber photometry research but do not have a computational background.

pMAT (Photometry Modular Analysis Tool), created by the Barker lab [41]pMAT is an open-source software suite developed in MATLAB for visualizing and analyzing fiber photometry data. It is designed to perform fundamental processing steps, including signal correction, normalization, and event-aligned analyses. pMAT is particularly accessible for researchers new to fiber photometry, offering a streamlined approach compatible with the most used data acquisition systems. The tool aims to promote consistency in data processing and serves as a step toward standardizing analysis practices across the field.

GuPPy, created by the Lerner lab [42], is a Python-based fiber photometry analysis tool designed to be accessible for new users, particularly those with limited coding experience. It features a graphical user interface that guides researchers through key analysis steps, making it easier to adopt without extensive programming knowledge. Unlike pMAT, which is MATLAB-based, GuPPy leverages Python—a freely available and open-source language—thereby reducing the cost barrier for users. Additionally, GuPPy offers the flexibility to modify and extend its functionality for those with more advanced coding skills to suit specific experimental needs.

FiPhA, created collaboratively between the Social & Scientific Systems, Inc., and the Neurobiology Laboratory of the National Institute of Environmental Sciences (NIEHS) [43], is an open-source fiber photometry analysis software developed using the programming platform R. It was designed to offer a robust, flexible, and visually intuitive interface for data analysis. FiPhA supports customizing input data formats, making it compatible with various fiber photometry acquisition modes. Notably, it allows researchers to analyze behavioral and photometry data within a single user interface, streamlining the workflow for integrated experimental analysis.

In addition to the three software packages mentioned, various research teams have developed other open-source and custom analysis tools. While these packages may vary in capabilities, they all share the goal of enabling the visualization and analysis of fiber photometry data, catering to a range of experimental needs and user preferences.

DISCUSSION

Comparing Fiber Photometry to Other Techniques

Fiber photometry builds upon existing neural technologies while offering additional benefits. In this way, it is a steppingstone between well-established techniques and novel discoveries. Below, we describe how

fiber photometry compares to two-photon microscopy, miniscopes, and single electrode/sharp electrode recordings.

Two-photonoton microscopy uses a scanning laser to emit femtosecond-pulsed near-infrared photons to excite a fluorophore. This allows for three-dimensional image resolution at the submicron scale [44, 45]. Like fiber photometry, genetically encoded indicators are used to detect and image neurons. Two photons of near-infrared light are absorbed by the fluorophore, combining to produce an excited state comparable to that of a single, higher-energy photon [46]. Two-photon microscopy achieves higher spatial resolution (submicron) than confocal microscopy because infrared light scatters less than visible light within tissue [47]. While fiber photometry allows for the investigation of deeper tissues, it can only record at a population level and requires further processing and analysis to create images. In contrast, two-photon microscopy achieves single-cell resolution and directly images cellular structures through an implanted lens [1, 48]. However, fiber photometry excels over two-photon microscopy is with its temporal precision. While the fiber optic captures fluorescent activity within milliseconds, two-photon microscopy imaging is limited by the speed of its scanning laser (tens of milliseconds), though improvements to imaging speed have been made [49]. A major caveat to two-photon microscopes is the requirement for the animal to be head-fixed. This limitation prompted the advent of miniscopes, an alternative neural imaging technique, which implements two-photon microscopy in freely moving mice [50, 51] and *Drosophila* larvae [52], and in combination with optogenetics [53].

Miniscopes were developed for imaging neural activity in freely moving animals. The original design was around 2.4 cm^3 and weighed 1.9 g [54]. The wires supplying power and transferring data to and from the miniscope are more flexible than fiber optics, and wireless miniscopes have been developed utilizing micro-SD storage cards and batteries attached to the device or a separate backpack to improve mobility further. [55-57]. Miniscopes use wide-field LEDs to excite fluorescent indicators, and the resulting image is recorded via a CMOS camera [54, 58]. The light passes through a gradient refractive index lens (GRIN), which can be placed directly on the brain's surface or mounted for slightly deeper imaging. Like two-photon microscopy, miniscopes are limited to imaging superficial layers of tissue, around 150 μm [58], though deeper imaging of around 500 μm is possible with the use of a mounted GRIN lens [59]. Compared to fiber photometry, miniscopes are bulkier, which limit some behavioral studies, especially those requiring motor tasks. Nonetheless, some longitudinal studies have been performed on rodents and even non-human primates [60, 61]

In contrast to the previously discussed imaging methods, single electrode, or sharp electrode, recording is an older electrophysiological method used to image single neurons [62]. Sharp electrode recordings use current or voltage clamping to measure intracellular changes in potential or current, respectively. The electrode comprises a glass micropipette, 1 μm or less in diameter, filled with an electrolyte solution of around 2 M [62, 63]. The molarity of this electrolyte solution must be matched with the molarity of the target cell to achieve the most accurate recordings [64, 65]. From these recordings, specific subtypes of

neurons can be identified based on firing patterns, activity duration, and waveform changes in response to stimulus [66, 67]. Leak conductance has been reported to attenuate signal, introduce noise and artifacts with sharp electrodes [68, 69], but qualitative identifying features do not appear to be significantly altered [70]. Due to the single-cell resolution of sharp electrodes, this technique has been the primary tool for describing neural function and has been seminal for understanding the activity of single neurons within brain regions or networks [71, 72]. Indeed, electrophysiology has been considered the "gold standard" in temporal resolution [73, 74]. However, sharp electrode recording generally requires a head-fixed, stereotaxic procedure that limits in vivo implications, unlike fiber photometry [63, 75].

Optogenetics, Chemogenetics, and Fiber Photometry

While fiber photometry has become increasingly favored over other electrophysiological techniques, it can also complement existing neural technologies. Optogenetics is a well-established technique that utilizes fiber optics like fiber photometry. However, rather than imaging a brain region, optogenetics manipulates [76-78]. When used with fiber photometry, brain regions and neuronal circuits can be studied bidirectionally (both functionally and connectivity-wise). Optogenetics involvesconnectivity-wise genetically encoded photosensitive proteins that can be expressed when exposed to light. When activated, these photosensitive proteins can either trigger or inhibit further activity [76, 79]. Optogenetics alone is often used to test how activation or inhibition of a brain region affects an event of interest [80]. However, when used with fiber photometry, the two techniques can be used to study how brain regions are connected both functionally and structurally [81]. To do this, a fiber optic is implanted in one brain region for optogenetic stimulation (i.e., the ventral tegmental area). In contrast, a second fiber optic is implanted in another brain region for fiber photometry imaging (i.e., the nucleus accumbens). To this end, when the optogenetic fiber is stimulated, the downstream activity in the connected brain region can be recorded and quantified. Advances in optogenetics and fiber photometry have made targeting specific cell populations possible for even greater selectivity. An alternative approach is to perform both optogenetics and fiber photometry in the same fiber optic [82]. This allows brain regions to switch from being the site of activation to the site of recording easily and spurs the study of bidirectional effects. Indeed, using optogenetics with fiber photometry has become a popular way to study neural circuits in a variety of applications [3, 81, 83-85].

Like optogenetic experiments, chemogenetics offers an alternative way to manipulate brain regions and circuits reversibly. However, whereas optogenetics allows for acute and temporally precise control of brain activity, chemogenetics may reflect more naturally occurring neural dynamics [86]. Chemogenetics utilizes genetically encoded receptors only activated by a specific ligand or chemical. Typically, these receptor-ligand combinations are designed to preserve natural signaling dynamics yet control the release of endogenous neurotransmitters [87-90]. Furthermore, these receptors can be stimulated to enhance or inhibit neural activity and can be selectively expressed by cell type [91]. While optogenetic studies have

primarily been conducted in rodent models, chemogenetics has been used in non-human primate studies [92, 93] and has gained popularity for the potential of human clinical use [87, 88, 94, 95]. Thus, implementing fiber photometry with chemogenetics has proven to be a fruitful combination. Studies that use fiber photometry to record chemogenetically influenced neural activity have bolstered our understanding of arousal, the brain-gut pathway, social behaviors, and depressive-like behaviors [96-99].

Using Fiber Photometry in Tandem with Behavior

Fiber photometry's most compelling feature is its ability to capture neural activity synchronized to awake, freely moving behavior [1, 5]This advantage over other neural imaging techniques has prompted many studies utilizing fiber photometry in tandem with existing behavioral tests. These studies have yielded novel findings in a variety of neuroscience fields, including social behavior, addiction, and mood affect (e.g., depression, and anxiety).

Social Behavior

Linking neural activity to social behavior has historically been challenging due to the complex nature of social interactions and the lack of an adequate way to study them. Several brain inputs are responsible for the display of social behavior, including the prefrontal cortex, anterior cingulate cortex, insular cortex, periaqueductal gray, medial preoptic area, ventral tegmental area, and nucleus accumbens [100-102]. Choosing which brain region or circuit to target is advised by the specific type or aspect of social behavior of interest (i.e., maternal behavior, social interaction, aggression, mating, motivation, hedonics, motor execution) [102]However, fiber photometry has enabled robust investigation of these brain regions' unique role during naturalistic social behaviors, producing novel findings.

Maternal behavior is an evolutionarily conserved expression of social behavior within altricial species. Yet despite the necessity of maternal behavior for offspring survival, the study of mother-infant interactions, the emergence of 'maternal instinct, and the neural correlations of such behavior are relatively under-researched. However, it is important to recognize the existing research conducted in humans, nonhuman primates, and rodents. In humans, the impact that being a mother has on cognition and the brain has been investigated using a variety of assays, including questionnaires, endocrine/ hormonal analysis, and later life brain health outcomes (i.e., neurodegenerative diseases, stroke) [103, 104]. In non-human primates, maternal behavior is observed naturally, allowing primate mothers to interact with their offspring with little human interference [105, 106]. In comparison, rodent models can more intimately investigate the convergence of neurological and hormonal changes during parturition and early postpartum. Indeed, rodent studies have contributed valuable knowledge to the field, including the identification of important neural circuitry, the patterns and effects of hormonal and neurochemical levels, and the role that epigenetics plays in the expression of maternal behavior [15, 16, 107-110]. The study of postpartum depression and anxiety has also been studied in both humans and rodents, as understanding the

neurological correlations of aberrant caregiving can help us prevent and treat such conditions [111-115]. Yet very little is known about real-time neural activity while maternal behaviors occur. Research that utilized fiber photometry during mother-pup interactions has begun to illuminate how maternal rodent brains react to pup cues (i.e., pup vocalizations)[81] and how their neurons activate while performing maternal tasks (i.e., pup retrieval) [116, 117]. These three papers examined simple yet fundamental aspects of caregiving. The novel photometry data have validated and expanded our knowledge of neural dynamics, and the unique circuitry activated during motherhood.

Social Behavior			
Publication	**Field**	**Method**	**Finding**
Valtcheva et al., 2023 [81]	Maternal Behavior	Mice: Maternal responses to pup cues. AAVDJ-CAG-FLEx-GCaMP6s injection in the PVN.	Pup calls release VTA oxytocin through PIL projections to the PVN.
Dvorkin & Shea, 2022 [116]	Maternal Behavior	Mice: Maternal pup retrieval. AAV5-Syn-Flex-GCaMP6s or AAV9-Syn-Flex-jGCaMP7f-WPRE injections into the LC.	Tonic LC firing encodes arousal whereas phasic LC firing promotes goal-directed behavior.
Xie et al., 2023 [117]	Maternal Behavior	Mice: Maternal pup retrieval. AAV-syn-FLEX-jGCaMP7f-WPRE injection in the VTA.	VTA DA neuron activity follows a reward prediction error model and does not directly mediate motivation or motor activity.
Dai et al., 2022 [83]	Maternal, Social Interaction, Aggression, and Mating	Mice: Maternal pup retrieval, social interaction (same sex), social interaction (different sex), and social defeat. AAV9.hSyn.DIO.GRAB$_{DA2m}$ or AAV9.hSyn.*loxP*.GRAB$_{DA2m}$.*loxP* injections into the NAc core.	NAc Core DA activity encodes distinct information during different phases (i.e., approach, investigation, and consummatory) of social behavior with sex differences.
Gunaydin et al., 2014 [147]	Social Interaction	Mice: Novel mouse interaction and novel object interaction. Custom GCaMP5g in a pAAV-EF1α-DIO-ChR2-YFP-WPRE frame injected in the VTA	VTA activity encodes and predicts social interaction. VTA activity differs during novel social and novel object interaction.
Guo et al., 2023 [14]	Aggression and Mating	Mice: Multifiber photometry during male aggressive and male mating behavior. AAV1-CAG-Flex-GCaMP6f-WPRE.SV40 or AAV2-CAG-FLEX-GCaMP6f-WPRE.SV40 injections into 5 hypothalamic regions, 5 amygdala regions, the LSv, SUBv, and lPAG	Increased limbic functional connectivity during social action initiation, but increased network dissociation during late copulation. Propose a mating-biased network and an aggression-biased network.
Chen et al., 2024 [148]	Aggression and Mating	Mice: Multifiber photometry during male aggression and male mating behavior. AAV1-CAG-FLEX-GCaMP6f or AAV2-CAG-FLEX-GCaMP6f injections into 5 hypothalamic regions, 5 amygdala regions, the LSv, SUBv, and lPAG.	Used linear dynamical system and hidden semi-Markov model to infer latent neural dynamics. Found unique brain activity associated with different behaviorally relevant states.
Yang et al., 2023 [146]	Aggression	Mice: Male aggression. AAV-hSyn-Flex-GCaMP6s injections into the VMHvl.	Subtype of male mouse hypothalamus neurons mirror aggressive behavior when observing a fight and are functionally important for displaying aggressive behavior.

Table 1. Selected publications that utilized fiber photometry to study various types of social behaviors.

More classical studies of social behavior include examining social play among juveniles and aggressive behavior, and mating behavior following sexual maturity. These three displays of social behavior appear in nearly all mammals and are essential to species survival. Juvenile play is typically rewarding and introduces complex aspects of social dynamics, which are thought to help foster relationships and establish group norms [3, 118-120]. Social play in human children is particularly fascinating as patterns of play can be used as developmental markers and can predict later life aptitudes or disorders (i.e., autism spectrum disorder) [121-123]. In non-human primates, the study of social play revolves around finding connections between play behavior and the establishment of social bonds and order [124-126]. Conversely, rodent research focuses less on the cognitive implications of play and more on the rewarding aspects of social interactions. [127-129]. Aggressive behavior has also been studied in human, non-human primate, and rodent populations to understand the purpose and expression of such interactions, as well as which brain regions or hormones are responsible [17, 130-137]. Finally, the biological and cognitive components of sexual behavior have been of interest for generations and have provoked hundreds of studies in humans and rodents to understand and potentially optimize mating [138-145]. Thus, it's no surprise that fiber photometry research in tandem with these aspects of social behavior (i.e., play, aggression, and mating) has recently emerged [14, 83, 146-148]These publications' findings have validated and challenged previously accepted ideas about the rewarding or aversive nature of specific social interactions.

Addiction

Addiction is a complex and multifaceted condition that affects millions of people worldwide. It is characterized by compulsive substance use or alterations in behavior despite negative consequences. Addiction is centered around the brain, where interconnected areas and neural circuits contribute to the development and maintenance of addictive behaviors. Having a comprehensive understanding of how addiction operates within the brain is essential for both effective treatment and prevention. An important aspect of addiction is the role of the reward system, specifically the mesolimbic pathway, which includes the nucleus accumbens, the pre-frontal cortex (PFC), and the ventral tegmental area (VTA), all of which are heavily involved in the processing of pleasure, motivation, decision-making, and inhibitory control. These brain regions are altered in addiction, which explains the compulsive nature of the behavior [19, 20]. The hippocampus and amygdala, typically implicated in memory and learning, play crucial roles by reinforcing addictive behaviors via associating substance use with positive feelings or stress relief [18]. The neurobiological changes that occur in these regions help explain why addiction is challenging to overcome, as it involves alterations in neural activity and long-term changes in brain circuitry. These brain changes reflect a process of learning and memory, often leading to appetitive drug-seeking behaviors [149, 150]. Furthering our understanding of the brain circuitry involved in addiction can enable researchers and clinicians to develop more targeted strategies, advance addiction treatment, and improve recovery

outcomes in the future. Below, we discuss a few publications that studied substance use with fiber photometry.

Addiction			
Publication	**Field**	**Method**	**Finding**
O'Neal et al., 2022 [151]	Conditioned Drug Associations: NAc	Rats: Conditioned Place Preference procedure. 1-3 mg/ml conc. of Heroin administered in doses of 1 mL/kg. 0.2 mg/ml conc. of Buprenorphine administered in doses of 1 mL/kg, Saline administered controls. dMSN infusions: AAV8-EF1α-fDIO-GCaMP6s in NAc. iMSN infusions: AAV1-Syn-FLEX-NES-jRCaMP1b-WPRE-SV40 in NAc.	dMSN Ca^{2+} signaling was stronger prior to entering heroin-paired context, weaker when exiting. iMSN Ca^{2+} signaling weaker prior to entering heroin-paired context, stronger when exiting.
Saint-Jour et al., 2025 [152]	Drug Administration: NAc	Mice: 15 mg/kg conc. of Cocaine administered in doses of 10 mL/kg. NAc injected with AAV-DIO-GCaMP3-NLS, D1R MSNs co-injected with a serotype 9 AAV-PPTA-Cre.	Cocaine administration induced rapid and sustained increases in Ca^{2+} levels within D1R MSNs.
Wei et al., 2018 [153]	Drug Administration: VTA and DRN	Mice: Nicotine, Heroin, Cocaine, and MDMA at varying doses injected according to animal weight. DAT-Cre mice infused in VTA, Sert-Cre mice infused in Dorsal Raphe with AAV serotype2/9 carrying DIO-GCaMP6m.	Heroin administration: DA receptor signals increased rapidly and sustained, SERT receptor signals increased at medium and high doses. Induced hyperactive locomotor behavior. Nicotine – Rapid spike in dopamine receptor signals followed by suppression and rebound at higher doses. No increase in locomotor activity. Cocaine – Dose-dependent increases in both DA and SERT receptor signaling, corresponding increase in locomotor hyperactivity. MDMA – Slow but sustained decrease in both DA and SERT receptors, stronger decrease in SERT receptors. Small effect on locomotor activity.
Jiang et al., 2024 [154]	Withdrawal: Mitochondrial Ca^{2+} signaling	Mice: Morphine injection of 10 mg/kg. Mitochondrial tracing utilized different variants of Adeno-associated vector (AAV)	Withdrawals disrupted dopaminergic neuron mitochondrial Ca^{2+} transport, resulting in mitochondrial fragmentation and reduced event frequency.
Tan et al., 2024 [155]	Withdrawal: VP	Rats: Infusion of 1mL of 0.75 mg/kg conc cocaine during SA training. Withdrawal following establishment of stable SA behavior. AAV2/9-hSyn-GCaMP6s-WPRE-pA injected in VP.	Increased activity in response to drug-related cues, suggesting a role in encoding motivational significance during abstinence.

Table 2. Selected Publications that utilized fiber photometry to study the administration of addictive substances.

In a heroin-conditioned place preference procedure, dopamine signaling and activity in the nucleus accumbens (NAc) direct pathway drive entry into the heroin-paired context, while the indirect pathway is

involved in existing the context. O'Neal et al. (2022) used fiber photometry to measure temporally precise dopamine signaling and activity of direct-pathway (dMSNs) and indirect-pathway (iMSNs) medium spiny neurons (MSNs) during heroin-context entries and exits [151]. They compared the signals recorded during these events to baseline data in control and experimental groups, before and after conditioning. The study employed a 415 nm control and 470 and 560 nm excitation signals to monitor dMSN and iMSN Ca^{2+} and dopamine signals. Results showed that DA and dMSN Ca^{2+} signaling were stronger when entering the heroin-paired context and weaker when exiting, while the reverse pattern was observed for iMSN Ca^{2+} signaling. [151].

Using fiber photometry to monitor nucleus accumbens (NAc) nuclear Ca^{2+} dynamics, Saint-Jour et al. (2025) found that D1R medium spiny neuron (MSN) Ca^{2+} signaling significantly increased approximately 5 minutes after cocaine injection, compared to saline-injected controls. [152]. This increase in activity continued to rise until it plateaued between 10 to 20 minutes post-injection. These results demonstrate that cocaine induces rapid and sustained increases in Ca^{2+} levels within D1R MSNs [152].

The effects of different drugs on midbrain dopamine (i.e., VTA) and serotonin (i.e., DRN) receptor activity were examined by tracking Ca^{2+} signaling in response to varying doses of heroin, nicotine, cocaine, and MDMA [153]. In the case of heroin, dopamine receptor Ca^{2+} signaling increased rapidly and remained sustained for up to an hour. At the same time, serotonin receptors showed significant increases in Ca^{2+} signals at median and high doses. This increase in Ca^{2+} signaling was associated with hyperactive locomotor behavior following a similar temporal pattern in dopamine and serotonin receptors. [153]. Nicotine induced a rapid spike in dopamine receptor Ca^{2+} signaling at all initial doses, followed by a brief suppression and

subsequent rebound to elevated levels with higher doses. Unlike heroin, however, nicotine did not increase locomotor activity [153]. Cocaine administration led to dose-dependent decreases in both dopamine and serotonin receptor Ca^{2+} signaling, with a corresponding increase in locomotor hyperactivity [153]. Finally, MDMA induced a slow but sustained decrease in Ca^{2+} signals in both dopamine and serotonin receptors, with serotonin receptors showing a stronger decrease. MDMA had only a small effect on locomotor activity [153].

Addiction and withdrawal from substances like morphine and cocaine lead to significant changes in brain regions involved in reward and motivation. Jiang et al. (2024) explored the impact of morphine withdrawal on dopaminergic neurons, showing that chronic morphine use disrupts mitochondrial Ca^{2+} transport, resulting in mitochondrial fragmentation and reduced Ca^{2+} event frequency. These changes were measured using mitochondria-targeted Ca^{2+} sensors (Mito-GCaMP) and fiber photometry to track fluorescence signals at 470 nm, highlighting withdrawal-induced impairments in intracellular signaling [154]. In contrast, Tan et al. (2024) used fiber photometry to monitor Ca^{2+} dynamics in the ventromedial ventral pallidum (VPvm) during cocaine withdrawal. They found increased Ca^{2+} activity in response to drug-related cues, suggesting a role in encoding motivational significance during abstinence. [155]. While both studies

utilize fiber photometry to capture real-time neural activity, they reveal distinct patterns of Ca^{2+} signaling across different brain regions and drug types, highlighting the technique's versatility in revealing the varied neurobiological effects of withdrawal.

These studies illustrate the complex and dynamic neural processes that underlie addiction, from initial drug exposure to withdrawal and relapse. Advanced techniques such as fiber photometry and calcium imaging enable researchers to capture real-time, cell-specific activity within key brain regions involved in reward, motivation, and decision-making. As this field advances, such insights will be critical for informing the development of more precise and effective interventions for substance use disorders.

Mood Affect

Fiber photometry has helped elucidate functional networks in the context of mood affect, particularly depression and anxiety. For example, activating specific receptors in the basolateral amygdala (BLA), a region known to be involved in anxiety [156-158], has been shown to produce differential anxiolytic effects in mice. Fiber photometry revealed how two specific circuits connecting the BLA with the prefrontal and insular cortices are organized and function, highlighting the importance of precise mapping of drug interactions while offering potential therapeutic targets [159].

Increased activity of glutamatergic neurons in the BLA is associated with depression-like behaviors, and their inhibition has been shown to alleviate such behaviors [160]. Using fiber photometry, researchers have been able to monitor the response of GABAergic neurons in the BLA of mice to stressful situations in real time. These neurons have an anxiolytic effect when active, and their activity was found to be reduced during tail suspension and chronic social defeat, common ways to model depression in animals [161, 162]. Another study built upon previous findings of increased acetylcholine (Ach) levels in both human patients with depression and animal models of depression [163, 164]. Using fiber photometry in conjunction with a genetically encoded sensor to monitor Ach levels, they found that higher Ach levels in the medial prefrontal cortex (mPFC) were linked to learned helplessness - a behavior resembling depression. Furthermore, pharmacologically increasing Ach levels strengthened the effect [165].

However, studying the ontology and neural correlations of depression and anxiety go hand in hand with the development of treatments for such mood disorders, yet the mechanism of action of antidepressants are, to this day, not fully characterized and hotly debated [166-169]. Monoamine reuptake inhibitors are effective for many patients, though the cause of delay in clinical onset is unknown [166]. Fiber photometry was used in one study to monitor the long-term effect of common and novel antidepressants on mPFC glutamatergic neuron activity in a mouse model of depression [170]. A reduction in depression-like behaviors coincided with increased activity in the mPFC. In another study using fiber photometry, the effects of fluoxetine, a selective serotonin receptor inhibitor (SSRI), and duloxetine, a selective norepinephrine reuptake inhibitor (SNRI), were recorded after onset of treatment [170]. The effects of duloxetine were apparent sooner than

fluoxetine, possibly owing to an increase in dopamine levels in the mPFC as suggested by Li et al., [171]. Dopamine's role in depression was further demonstrated in research using non-invasive brain stimulation. Fiber photometry was used to track dopamine activity in the ventral tegmental area (VTA), showing that depression-like behavior was linked to lower activity [172].

Mood Affect			
Publication	**Field**	**Method**	**Finding**
Asim et al., 2024 [161]	Anxiety & Depression	Mice: BLA activity during foot shock, tail suspension, and social interaction with an aggressor. Bilateral injection of BLA with various GCaMP6s	BLA GABAergic neurons decrease activity during stressful situations. Activation attenuates depression-like and anxiety-like behaviors.
Abdulla et al., 2024 [165]	Depression	Mice: Ach activity in the mPFC during learned helplessness and active avoidance. AAV9 hSyn-ACh4.3 injection in the left hemisphere of the mPFC	mPFC Ach levels positively correlate with escape deficit in the active avoidance task.
Yan et al., 2024 [170]	Depression & Antidepressants	Mice: mPFC activity during forced swim test. Effects of five antidepressants (fluoxetine, duloxetine, ketamine, vilazodone, YL-0919) on depression-like behavior. AV-CaKIIa-GCaMP6s-WPRE-hGH-pA injection in mPFC	Increase of Ca2+ activity in mPFC pyramidal neurons coincides with the onset of antidepressant effects; duloxetine (SNRI) onset is quicker than fluoxetine (SSRI).
Choi et al., 2024 [172]	Depression & Vagus Nerve Stimulation	Mice: VTA dopamine activity with or without transcutaneous auricular vagus nerve stimulation (taVNS) in a forced swim paradigm AAV-Flex-jGCaMP8f injection in VTA	taVNS resulted in a decrease in immobility time during the forced swim test, which was correlated with increased dopaminergic VTA activity.
Yin et al., 2024 [180]	Depression & Ketamine	Mice: Serotonin activity in mPFC during the tail suspension test, 60 min or 24 hr. post ketamine treatment; *Tph2* knockout to inhibit serotonin synthesis in one group rAAV-hSyn-5HT2.1-WPRE-hGHpA injection in mPFC	Increased serotonin activity 24 hr. after ketamine treatment negatively correlates with immobility time, suggesting a sustained antidepressant-like effect. But an increase in serotonin was not seen in the first 60 min after the ketamine dose, and Tph2 knockout exhibited sustained but not immediate antidepressant effects. Suggests that other neurotransmitters may be involved.
Yokoyama et. Al, 2024 [186]	Social Isolation & Ketamine	Mice: Anterior insula activity of mice raised in social isolation during a three-chamber test AAVdj-CaMKIIa-GCaMP6f-P2A-nls-dTomato injection in the right anterior insula cortex	(R)-ketamine, but not (S)-ketamine, increases anterior insula activity in mice raised in social isolation upon interacting with a stranger mouse.

Table 3. Selected Publications that utilize fiber photometry to study anxiety, depression, and the effects of various kinds of antidepressant treatments.

In addition to the classic SSRI and SNRI antidepressants, there has been a recent interest in the antidepressant effects of the N-methyl-d-aspartate receptor (NMDAR) antagonist ketamine [173-178].

Fiber photometry has proven useful in determining the brain regions and neurotransmitters involved in ketamine's depression-alleviating effects. Serotonin is arguably the most widely researched neurotransmitter implicated in depression [179] and was found to increase in the mPFC after a single injection of ketamine, which was correlated to a decrease in depression-like behavior in mice [180]. Interestingly, even when a gene responsible for serotonin synthesis was removed [181], ketamine still had an antidepressant effect, suggesting serotonin modulation might not be the underlying mechanism [180]. Significantly, ketamine also affects the dopaminergic system, providing another route for study [182, 183]. Fiber photometry has been employed to address previous studies' poor temporal resolution [184] and explore the varying effects of ketamine enantiomers [185]. One study with socially isolated mice showed that (R)-ketamine increased activity in the anterior insula [186], a region involved in social and emotional awareness [187, 188]. The increased activity occurred during social interaction and was not observed for (S)-ketamine [186]. This suggests (R)-ketamine as a possible treatment for social withdrawal symptoms, which are predictors for depression [189-191].

These studies demonstrate that fiber photometry's ability to record neural activity in freely moving animals helps bridge the gap between molecular and behavioral research in mood affect. Importantly, fiber photometry has confirmed previous findings and challenged others, ultimately increasing our understanding of the neural correlation behind depression and anxiety. Thanks to its low barrier to entry, we can expect fiber photometry to continue to illuminate the networks involved in mood disorders and will highlight the mechanisms behind traditional and novel therapeutic pharmaceuticals.

CONCLUSION

The divergent evolution of fiber photometry has aided its application within a variety of fields. Here we discussed how fiber photometry has built upon existing neural techniques and has been implemented in tandem with others to expand our capabilities of studying the brain. Additionally, we discussed fiber photometry's applications within the fields of social behavior, addiction, and mood affect. These three fields share an association with the reward and motivation circuit and the circulation of dopamine; however, fiber photometry has been used to study other neural networks and neurotransmitters beyond this. From its inception as a calcium indictor to its most recent adaptations, fiber photometry has revolutionized how researchers study specific brain regions and circuits. To this end, this technique sits at the crux of neuroscience research and serves as both a steppingstone from early forms of neural imaging towards even greater scientific discovery, and as a junction to connect and enhance existing techniques.

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