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Current perspectives on incentive salience and applications to clinical disorders

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Abstract

Affective neuroscience research has revealed that reward contains separable components of 'liking', 'wanting', and learning. Here we focus on current 'liking' and 'wanting' findings and applications to clinical disorders. 'Liking' is the hedonic impact derived from a pleasant experience, and is amplified by opioid and related signals in discrete sites located in limbic-related brain areas. 'Wanting' refers to incentive salience, a motivation process for reward, and is mediated by larger systems involving mesocorticolimbic dopamine. Deficits in incentive salience may contribute to avolitional features of depression and related disorders, whereas deficits in hedonic impact may produce true anhedonia. Excesses in incentive salience, on the other hand, can lead to addiction, especially when narrowly focused on a particular target. Finally, a fearful form of motivational salience may even contribute to some paranoia symptoms of schizophrenia and related disorders.

INTRODUCTION

A fundamental question in affective neuroscience is how reward is generated in the brain. Answers may provide valuable insight not only into normal reward experiences, but also into how dysfunction in reward mechanisms contributes to neuropsychological disorders such as drug and behavioral addictions, major depressive disorder (MDD), Parkinson's disease (PD), and schizophrenia. Reward contains major components of 'liking' (hedonic pleasure), 'wanting' (incentive salience or motivation), and learning, and we will focus here especially on relations between 'liking' and 'wanting. Research has indicated these two components are dissociable, and mediated by separable neural substrates. Here, we consider these components, and their application to reward dysfunctions.

'LIKING' AND 'WANTING' AS SEPARATE ASPECTS OF REWARD

In ordinary experience, 'liking' and 'wanting' seem conjoined. For example, we eat cake because we enjoy it, and often eat more than intended if the cake tastes good. However,

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brain processes underlying liking and wanting can sometimes cause these components to diverge in certain circumstances.

'Liking' (in quote marks) refers to the hedonic impact derived from a stimulus (which can be conscious or unconscious) [1,2]. Consciously, it corresponds to subjectively experienced pleasure commonly denoted by liking (without quote marks). An objective form of 'liking' reaction has been measured in affective neuroscience studies of rodents using the taste reactivity (TR) test based on hedonic facial expressions to taste, first developed in human infants by Steiner [3] and later adapted for rats by Grill and Norgren [4]. The taste-elicited orofacial reactions are homologous across many species, including rodents, apes, and humans [3,5]. For example, sweetness causes positive, appetitive orofacial reactions (e.g. tongue protrusions), which represent a 'liked' tastant. Alternatively, bitterness elicits aversive, negative orofacial reactions (e.g. gapes) and reflects 'disgust' (Figure 1A). Importantly, 'liking' can be distinguished from the sensory properties of a stimulus, such as sweetness. For example, when a sweet food that was once 'liked' is now disliked after being paired with visceral illness- a phenomenon known as conditioned taste aversion (CTA) [6–9]. Similarly, physiological states may shift hedonic tone, called alliesthesia [10], in which food may become more 'liked' when one is hungry [10] or even tasty chocolate can become less 'liked' when satiated [11].

'Wanting', or incentive salience, refers to attention-grabbing and motivational features of rewards and their learned cues [12]. Reward cues have the ability to often trigger bursts of reward-seeking motivation [13,14], and the cue itself becomes attractive as a 'motivational magnet'. Cue 'wanting' can be experimentally tested using the Pavlovian autoshaping or sign-tracking test [15,16], or in conditioned reinforcement tests where instrumentally working can earn cue presentations [17], and cue-triggered spurts of reward seeking are often experimentally tested using the Pavlovian Instrumental Transfer (PIT) test [13,18].

SEPARATE NEURAL SUBSTRATES MEDIATE 'LIKING' AND 'WANTING'

Liking in the brain

Research in our laboratory has identified a network of discrete sites, called 'hedonic hotspots', within limbic-related brain structures in which pleasure amplification mechanisms are localized (Figure 1B) [5]. For example, one hedonic hotspot can be found in the anterior-dorsal portion of the medial shell of the nucleus accumbens (NAc). Within hedonic hotspots, microinjection of opioid-stimulating drugs or a few other agents can enhance positive 'liking' reactions to sucrose taste [19–23]. Other subcortical hedonic hotspots have been found in the posterior portion of the ventral pallidum (VP) [24,25], and near the brainstem parabrachial nucleus of the pons (PBN) [26]. Recent findings have also identified two cortical hotspots: one in the anterior orbitofrontal cortex (OFC) and another in posterior insula [27], consistent with human neuroimaging findings that implicate these cortical regions in pleasure and/or disgust [11,28,29].

Notably, enhancement of hedonic reactions is restricted to these hotspots- the boundaries of which are defined by measuring the extent of neuronal activation surrounding the microinjector or optic fiber tip (known as 'Fos plumes'; Figure 2). Opioid microinjections

beyond hotspot boundaries do not enhance 'liking' reactions, even in the same structure and even if they still amplify 'wanting' to eat the reward. In some oppositely-valenced hedonic coldspot sites, opioid stimulation may instead produce the opposite suppression of 'liking' reactions to sweetness, even while still amplifying 'wanting' to eat [19,24,27].

Among hedonic hotspots, the posterior VP is the only known one where neuronal damage induced by lesions causes a loss-of-function elimination of positively valenced 'liking' reactions to sweetness and replacement with negatively valenced 'disgust' reactions [30–32]. This unique feature suggests that the VP hotspot not only amplifies 'liking', but is necessary for the expression of normal levels of 'liking' reaction.

Additionally, several hedonic hotspots appear to be functionally linked together, so that stimulation of one hotspot leads to activation of the others, indicating that the entire network acts as an integrated whole circuit to enhance 'liking' [27,33,34]. Moreover, unanimous activation of hotspots appears to be required for enhancing 'liking', as blocking opioid signaling in one hotspot prevents the opioid stimulation-induced enhancement of 'liking' reactions by another hotspot [33]. Together, these findings indicate that these hotspots form a larger functional circuit that underlies hedonic reactions.

'Wanting' in the brain

Incentive salience or 'wanting' is powered by a much larger mesocorticolimbic network of brain structures, and often involves a hyperactive mesolimbic dopamine system (Figure 1B) [35]. Despite its early label as a pleasure neurotransmitter, dopamine has never enhanced 'liking' in our studies, even in hedonic hotspots, and is no longer so widely thought to mediate pleasure. Instead, it is well known that presentation of previously learned reward cues activates midbrain DA neurons, causing release to a large network of structures, spurring the individual to action, and invigorating reward-seeking [35,36]. Structures involved in incentive salience include the ventral tegmentum containing dopamine neurons, the entire NAc, much of the dorsal neostriatum, the central amygdala (CeA), lateral hypothalamus (LH), OFC and other parts of prefrontal cortex, and VP, among others [37–39].

Beyond generating 'wanting', this circuitry also focuses motivation on particular targets. This allows one to adaptively 'want' different rewards at different times, but can be biased towards one particular target in addiction. Focusing of incentive salience may involve mesocorticolimbic interactions with amygdala. For example, our lab has found that pairing a particular sugar or cocaine reward with optogenetic laser-excitation of the central nucleus of amygdala narrowly focuses excessive 'wanting' on just that laser-paired reward (Figure 3) [38,40]. We think something like an equivalent neural change may happen without laser in the brain of addicts to focus 'wanting' on a particular addictive target.

Normally, focusing of 'wanting' is sensitive to current neurobiological and physiological states, allowing for appetites, satiety and other factors to direct craving [37,41]. In human addicts, states of intense stress, or drug exposure may also magnify cue-elicited 'wanting' to generate even more intense desire in particular encounters [42–44]. Related to stress, findings from our lab suggest corticotrophin-releasing factor, a brain stress-related

neurotransmitter, can amplify cue-triggered ‘wanting’ in some brain structures similarly to dopamine stimulation [45].

BLUNTED INCENTIVE SALIENCE AND THE ANHEDONIA PARADOX

Anhedonia (also termed consummatory anhedonia), or the inability to experience pleasures, has long been considered a defining symptom of some neuropsychological disorders, such as major depression (MDD), Parkinson’s disease (PD), and the negative symptoms of schizophrenia [46–52]. [53–55]. However, a number of clinical investigators have recently suggested that these patients have signs of avolition (sometimes called anticipatory anhedonia in clinical settings), or a lack of motivational ‘wanting’, instead of an actual lack of ‘liking’ or pleasure capacity [56–60]. For example, recent evidence has emerged to suggest that when liking is measured specifically, patients with these conditions exhibit no deficits in rating sensory pleasures such as ice cream [56,61–68], which suggests intact ‘liking’. Patients with these disorders do, however, fail to value those and other rewards in life. Accordingly, a hypoactive dopamine system of incentive salience has been implicated with each of these disorders [49,51,69]. Together, these interpretations are consistent with our understanding of the role of dopamine in ‘wanting’ but not ‘liking.’

Why have such deficits been characterized for so long in medical textbooks as anhedonia, rather than as avolition? One possibility is that traditional clinical measures of anhedonia do not adequately parse ‘liking’ from ‘wanting’, but rather blend them together. Indeed, the presence of anhedonia is often determined by patient self-report in that they expect rewards to have little value [70–72]. Patients’ ability to separate self-reports of ‘liking’ versus ‘wanting’ may be limited without careful questioning [73]. Even the newest generation of the DSM, for example, may not adequately differentiate between ‘liking’ and ‘wanting’ as it defines anhedonia as “lack of enjoyment from, [or] engagement in…life’s experiences…” [74] - with enjoyment resembling ‘liking’ and engagement reflecting ‘wanting.’ Together, these oversights may contribute to inconsistencies in the literature [67,75,76].

We applaud those researchers of depression, Parkinson’s disease, and schizophrenia who have addressed the potential dissociation between ‘liking’ and ‘wanting’ by adopting separate terms for each, such as anhedonia and avolition [59,77–80]. More specific definitions may assist clinicians in better differentiating between these symptoms, which, in turn, could lead to more accurate diagnoses and eventually allow more targeted and efficacious treatments.

HEIGHTENED INCENTIVE SALIENCE

The original clinical application of ‘wanting’ and ‘liking’ dissociation was to drug addiction, based on evidence that drugs of abuse can sensitize mesolimbic dopamine systems of incentive salience in vulnerable individuals [81]. According to that Incentive Sensitization Theory, drug addiction is characterized by a hyper-reactive mesolimbic dopaminergic system in response to drug reward cues, causing excessive cue-triggered ‘wanting’ to take more drugs [35]. Genetic and environmental susceptibilities to dopamine sensitization, coupled with repeated bingeing of drugs, can sensitize the mesocorticolimbic system of

particular individuals to create addiction [42,82]. In an extension of the incentive sensitization theory beyond drugs to behavioral addictions, recent neuroimaging studies have shown that a sensitization-like dopamine hyper-reactivity brain signature may also arise in some individuals without need of drugs, resulting in compulsive pursuit of other incentives such as gambling, sex, shopping, etc. [83–87].

For example, applied to gambling addiction, a recent fMRI study looking at cue reactivity to a food or gambling cue revealed that individuals diagnosed with gambling disorder demonstrated a greater change in activity of reward-regions in response to gambling cues than food cues, unlike in moderate gamblers who are not 'addicted' and less activated by the gambling cue [88]. Similarly, applied to sex, brain mesolimbic activations elicited by cues that predict a pornographic image elicited stronger mesolimbic brain activations and quicker reaction times in individuals with problematic pornography use (PPU) that rises to arguably compulsive levels than in non-compulsive users, which was interpreted by the investigators as consistent with incentive-sensitization [89].

Some of the most striking evidence that dopamine stimulation can produce behavioral addictions has recently come from dopamine dysregulation syndrome in medicated Parkinson's patients. For example, approximately 17% of patients with PD receiving medication that stimulates dopaminergic systems, especially high doses of direct agonist drugs that directly stimulate dopamine D2/D3 receptors, report the emergence of a new behavioral addiction, such as compulsive levels of gambling, shopping, sex, eating, hobbies, etc. [90]. Behavioral addictions may be magnified in early onset PD, in which upwards of 50% may develop an impulse control disorder involving behavioral addictions [91]. Further, some PD patients with this disorder also addictively over-consume their dopamine-stimulating medication, despite such medications not being reported as producing much pleasure [91–93]. Human imaging studies have pointed to excessive incentive salience via heightened mesocorticolimbic reactivity important for impulse control disorder development and addictive-like disorders [94,95].

CAN INCENTIVE SALIENCE FLIP TO FEARFUL SALIENCE IN PARANOIA?

Finally, a very different side of incentive salience, flipped to negative valence as an active-coping form of fearful salience may be manifested in motivational features of psychostimulant-induced psychosis and schizophrenic psychosis. Our laboratory has shown that excessive incentive salience generated by dopamine-glutamate interaction in the NAc can be flipped to a negative form of fearful salience [96–99]. Fear-biased generation caused by drug microinjections (e.g., AMPA antagonist, DNQX) that alter local glutamate-dopamine interactions occurs especially in posterior sites of NAc medial shell. However, most of the rest of NAc shell can also be recruited for fear generation in stressful situations, retuning the NAc's normal keyboard gradient of motivational valence (whereas comfortable environments bias the NAc manipulations towards generating positive incentive salience; Figure 4) [100,101]. Dopamine in NAc shell is crucial for generation of both incentive salience and fearful salience generated by these microinjections [102]. In particular, fearful salience especially needs D2/D3 dopamine receptor stimulation in NAc, whereas D1 receptor stimulation participates in both motivations [103].

In a major hypothesis of human schizophrenia, Kapur and colleagues have suggested that elevated dopamine signaling in striatum and NAc may underlie excessive motivational salience assigned to innocuous stimuli, resulting in their gaining excessive meaningfulness and even taking on a threatening aspect to the patient [104–107]. Indeed, there is strong evidence to suggest that hyperdopaminergic activity in striatum underlies these positive symptoms seen in schizophrenia, making them more motivationally compelling, even if the hallucinations or delusions themselves arise from other neural causes [104]. For example, higher dopamine metabolite levels in striatum is associated with greater positive symptoms [108], and levels of released striatal dopamine are almost doubled in schizophrenia compared to controls [109,110]. Elevating dopamine levels even in healthy humans, such as taking high doses of amphetamine or other psychostimulants, can sometimes lead to drug-induced psychosis and paranoia symptoms similar to schizophrenia [111]. Conversely, antipsychotic medications that generally block D2 receptors (though some also block serotonin receptors) may reduce paranoia symptoms in schizophrenia [92]. As Kapur and colleagues have suggested, it is conceivable that dopamine dysregulation in striatum resulting in abnormal dopamine release may lead to an aberrant assignment of salience to neutral stimuli [105,106]. Thus, psychosis may appear as a result of dopamine dysregulation in combination with other factors relevant to cognitive and sociocultural context.

Aberrant salience for some authors may mean simply exaggeration in attentional, physical sensory, or novelty/surprise features of stimulus perception, without any distorted motivational component. Such attentional salience has sometimes been posited to be mediated by phasic (rather than tonic) dopamine signals [112], or by early stages of a phasic dopamine signal, and that the later stage of the phasic signal encodes reward prediction error [113]. Other views have suggested that only some midbrain dopamine neurons encode reward prediction error value while different dopamine neurons encode motivational salience for both reward-related or aversive-related stimuli [114]. We note that views of aberrant salience as purely sensory/attentional, or of dopamine as prediction error teaching signals or hedonic values of reward, are distinct from our hypothesis that dopamine can mediate incentive/fearful salience independently from sensory features, prediction error learning, or hedonic reward values of stimuli [115], and different from motivational interpretations of aberrant salience in psychosis.

However, an additional motivational component of aberrant salience in schizophrenia has been posited by Kapur, Howes and their colleagues, and especially linked to striatal dopamine hyper-reactivity [104–107]. For example, as Howes and Nour [107] describe in a recent review, “the aberrant salience hypothesis of schizophrenia proposed that disordered mesostriatal dopamine release results from over-attribution of meaning and motivational value (incentive salience) to irrelevant environmental events” (p. 3). Elevated limbic reactivity to reward-related stimuli related to incentive salience may even precede full-blown psychosis. For example, Winton-Brown and colleagues [115] report “During reward anticipation, ultra-high risk [for psychosis] subjects showed greater activation than controls in the VP bilaterally” (p. 1) (but not during aversive anticipation or to neutral stimuli). Dopamine antagonist medications for psychosis are suggested by this group specifically to reduce excessive motivational salience: as Bolstad and colleagues [116] put it, the “… increased activity of the dopaminergic mesolimbic motivational system results in an aberrant

assignment of salience in patients with schizophrenia, and antipsychotic drugs are thought to relieve positive symptoms by dampening this aberrant salience through diminishing the dopaminergic hyperactivity" (p. 2259). All these views of aberrant salience and dopamine in psychosis expressed by Kapur, Howes and colleagues seem quite consistent with our view described above of the role of mesolimbic dopamine in incentive salience and fearful salience.

CONCLUSION

As a modular process, reward is best understood when 'liking' and 'wanting' components can be examined independently. In the affective neuroscience laboratory, experimental tools have disentangled these components in animal studies in order to probe their underlying neurobiological mechanisms. In human clinical populations, these findings seem to be having increasing applications to better understand reward dysfunction in depression, addiction, schizophrenia and other conditions. A greater understanding of reward components and their mechanisms thus may continue to facilitate strategies to understand and treat these complex human psychopathologies.

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HIGHLIGHTS

- Reward is a modular process that can be broken down into smaller components, including ‘wanting’ (incentive salience) and ‘liking’ (hedonic impact).
- Dopamine is necessary for ‘wanting’ but does not contribute to ‘liking.’
- Hypoactivity in dopamine-related systems may produce avolition (i.e. blunted ‘wanting’), a symptom common among patients with depression.
- Hyper-reactivity in sensitized dopamine-related systems of addicts may intensify ‘wanting.’
- Dysregulated dopamine signaling in the nucleus accumbens may assign fearful salience to otherwise neutral stimuli observed in patients with paranoid psychosis.

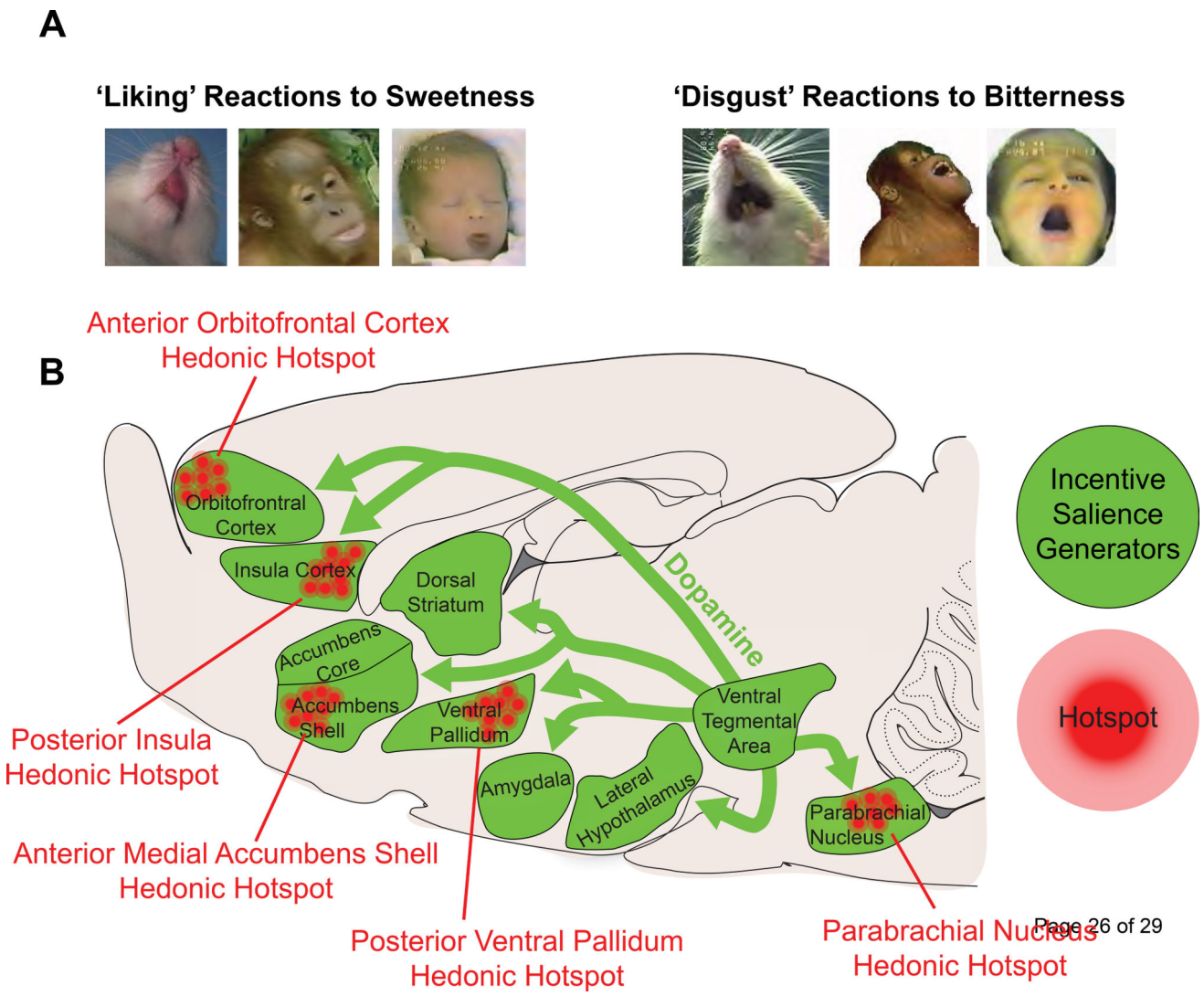

Figure 1.

Reward systems in the brain. **(A)** Examples of positive hedonic orofacial reactions ('liking') in response to the taste of sweet sucrose (left). Negative affective reactions ('disgust') in response to the taste of bitter quinine solution (right). These affective orofacial reactions to tastes are conserved across species in rodents, non-human primates, and humans infants. **(B)** Sagittal view of a rat brain depicting brain reward systems. Discrete sites, known as hedonic hotspots (clusters of red circles), can enhance 'liking' through the actions of opioids, endocannabinoids and orexins, but not dopamine. 'Wanting' is derived from dopamine signaling (green arrows), originating from the ventral tegmental area, acting in brain areas that generate incentive salience (purple structures). Hyperactivity in this 'wanting' circuit underlies many conditions characterized by excessive motivation, such as addiction, whereas hypoactivity (depicted by the smaller, darker arrows) may produce avolition seen in depression. Finally, aversive dysfunction of this 'wanting' circuit, particularly signalling onto the nucleus accumbens shell, may promote fearful salience to otherwise neutral stimuli- a trait commonly observed in patients with paranoid psychosis.

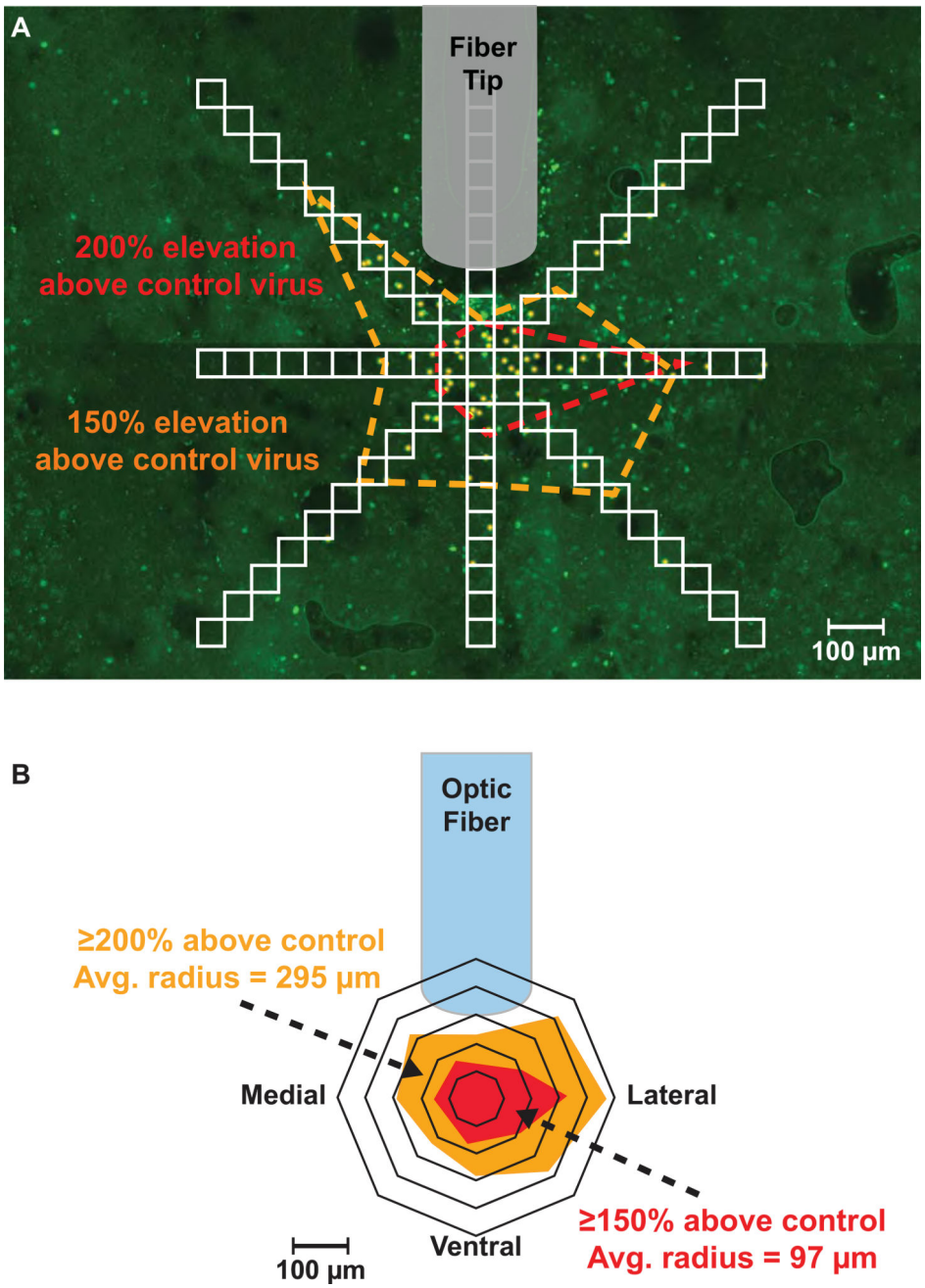

Figure 2.

Example of a 'Fos plume' produced by laser stimulation of local brain tissue containing channelrhodopsin (ChR2; excitatory optogenetic construct). Laser illumination of ChR2 stimulates expression of the immediate early gene, Fos (a marker of neuronal activity), in neurons immediately surrounding the optic fiber tip. **(A)** To measure Fos plumes, a radial grid of contiguous 50 µm squares is placed over a photomicrograph containing the area of the brain surrounding the tip of the optic fiber. Expression of Fos is quantified by counting the number of Fos immunoreactive neurons found within each square of the grid (yellow points). Comparing the degree of Fos expression in treatment animals relative to that of

control animals, which receive laser illumination but lack the optogenetic ChR2 construct, provides a means to measure the percentage in ChR2 laser-induced enhancement of neuronal activity relative to baseline (red dotted line = 200% control; orange dotted line = 150% control). **(B)** An average Fos plume is created by mapping the mean diameter of Fos elevation over baseline in each direction around the center. These Fos plumes provide highly objective and neuroanatomically precise information of where a laser stimulation or drug microinjection acts on the brain to enhance ‘liking’ and/or ‘wanting.’

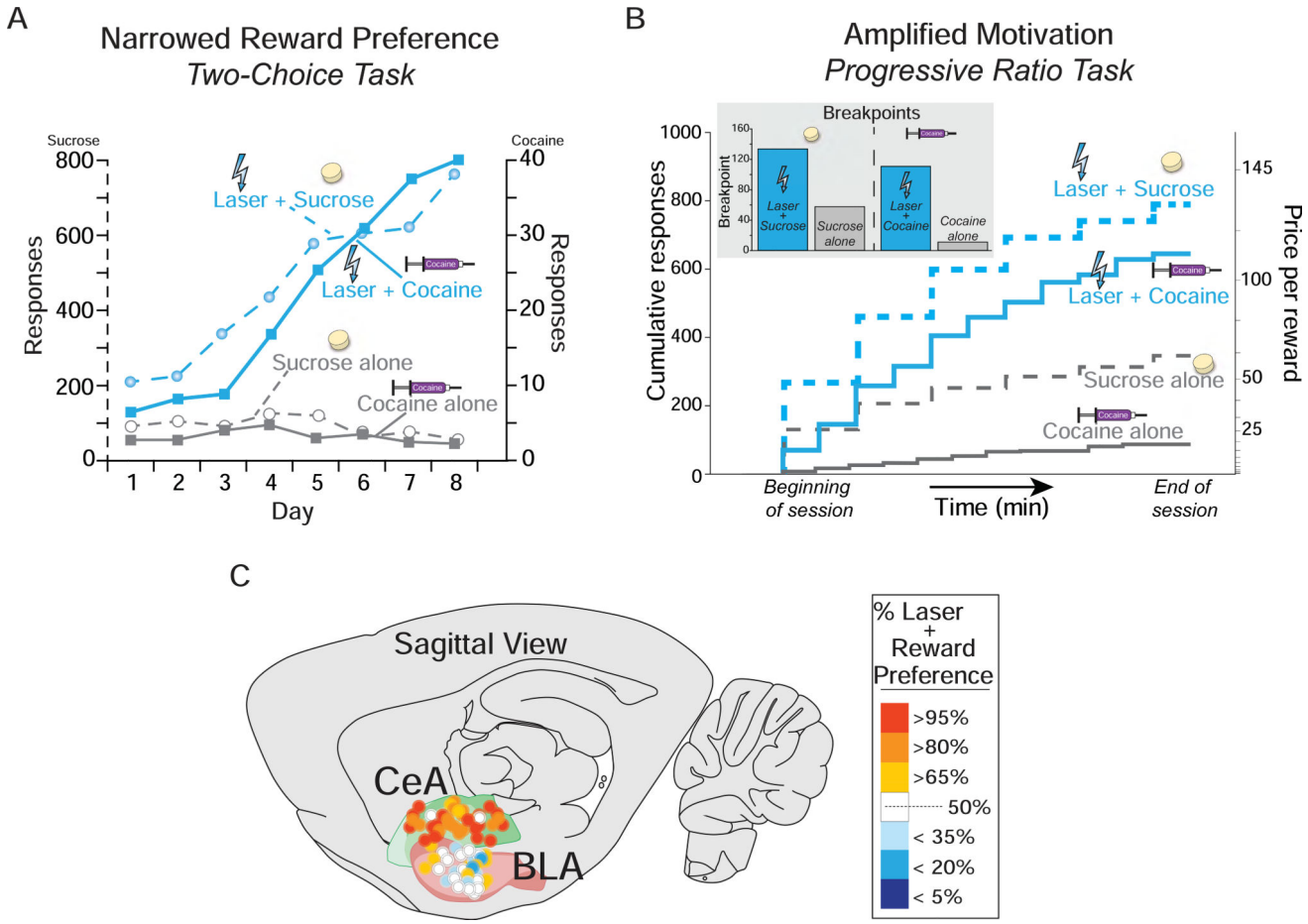

Figure 3.

Central Amygdala optogenetic ChR2-pairing narrows and amplifies reward choice. **(A)** When given the choice between earning a sucrose reward alone (grey circles and dashed lines) or earning a sucrose reward paired with optogenetic central amygdala (CeA) ChR2 stimulation (blue circles and dashed lines), rats intensely prefer the CeA-paired sucrose reward above and beyond the sucrose reward alone. When given the choice between earning a cocaine reward alone (0.3mg/kg/infusion; grey squares and solid lines) or earning a cocaine reward paired with optogenetic CeA stimulation (blue squares and solid lines), rats prefer the CeA-paired cocaine above and beyond cocaine alone. **(B)** In a breakpoint test of motivation intensity, rats are willing to work harder in a progressive ratio task, reaching higher breakpoints when laser is paired with rewards. **(C)** Notably, narrowing of motivation produced by optogenetic laser stimulation was observed in the CeA, but not the basolateral amygdala (BLA). Figure modified from [38] and [40]. CeA, central amygdala; BLA, basolateral amygdala.

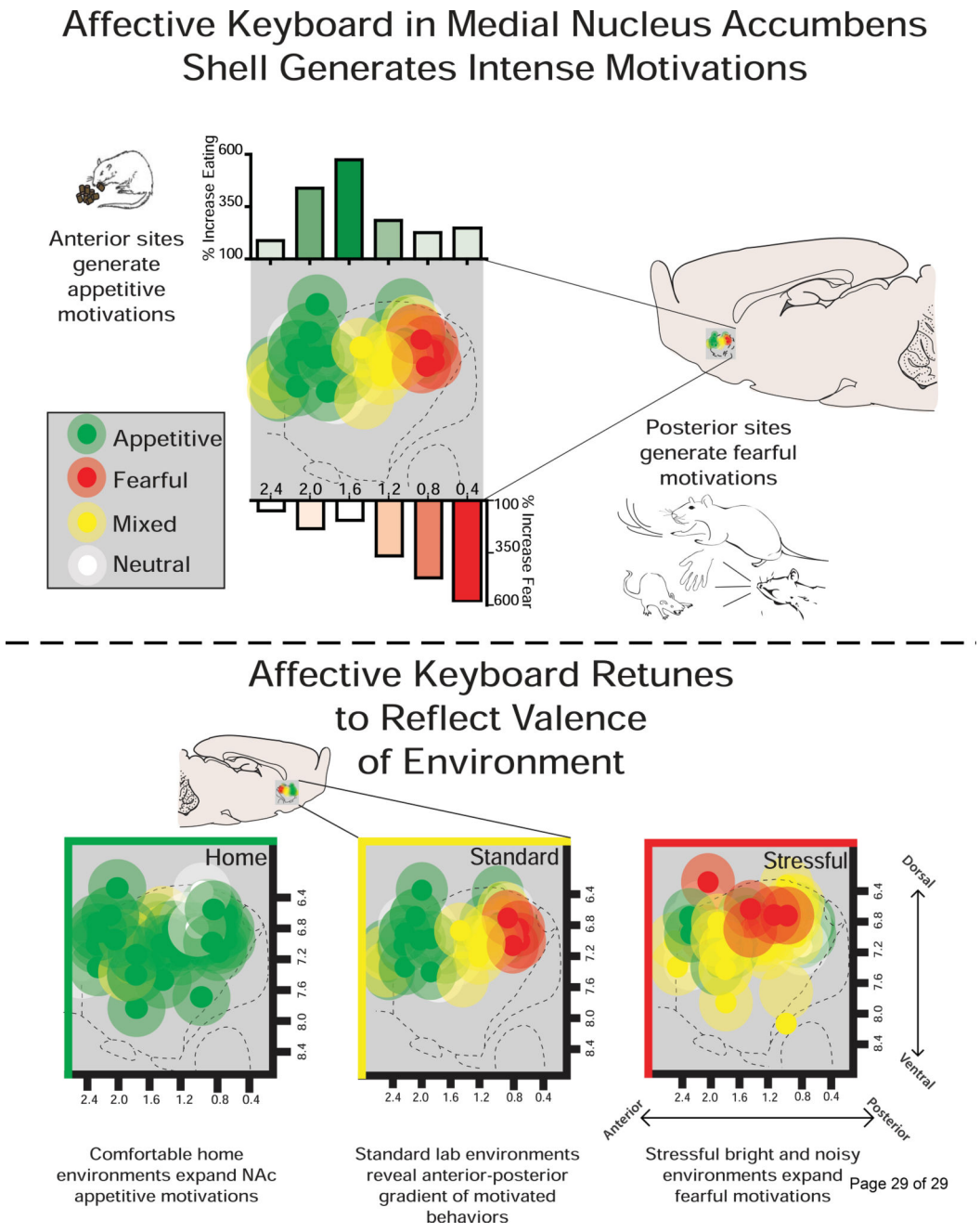

Figure 4.

Desire and dread in the nucleus accumbens. **(A)** Disrupting glutamatergic and/or dopaminergic activation in the medial nucleus accumbens shell reveals a anterior to posterior gradient of intense motivations. Microinjections of glutamate and/or dopamine antagonists in more anterior sites generate appetitive motivations (depicted in green) such as increased food intake. The same microinjections targeted posteriorly reveal fearful motivations (depicted in red) such as increased escape attempts, defensive treading, and vocalizations or bites toward experimenter. **(B)** The valence of the environment the rat is tested in reveals 'retuning' of the affective keyboard. When the same microinjections are given in a

comfortable home environment, appetitive motivations span caudally and replace fearful motivations with appetitive motivations. On the contrary, stressful environments equipped with bright lights and loud music reveals an affective keyboard with more fearful/mixed motivations replacing appetitive motivations.