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REVIEW ARTICLE

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Net gain and loss: influence of natural rewards and drugs of abuse on perineuronal nets

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Overindulgence, excessive consumption, and a pattern of compulsive use of natural rewards, such as certain foods or drugs of abuse, may result in the development of obesity or substance use disorder, respectively. Natural rewards and drugs of abuse can trigger similar changes in the neurobiological substrates that drive food- and drug-seeking behaviors. This review examines the impact natural rewards and drugs of abuse have on perineuronal nets (PNNs). PNNs are specialized extracellular matrix structures that ensheathe certain neurons during development over the critical period to provide synaptic stabilization and a protective microenvironment for the cells they surround. This review also analyzes how natural rewards and drugs of abuse impact the density and maturation of PNNs within reward-associated circuitry of the brain, which may contribute to maladaptive food- and drug-seeking behaviors. Finally, we evaluate the relatively few studies that have degraded PNNs to perturb reward-seeking behaviors. Taken together, this review sheds light on the complex way PNNs are regulated by natural rewards and drugs and highlights a need for future studies to delineate the molecular mechanisms that underlie the modification and maintenance of PNNs following exposure to rewarding stimuli.

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INTRODUCTION

The extracellular matrix (ECM) surrounds neurons both loosely and also in highly-specialized structures called perineuronal nets (PNNs) [1] to direct changes in synaptic morphology that are critical for neuronal plasticity [2–5]. Activity-dependent changes in organization of the ECM alter synaptic architecture and physiology in a way that changes synaptic transmission [2, 6–9]. PNNs are densely organized ECM components generated by neurons and glia that ensheathe specific neuronal cell bodies and proximal dendrites with holes at the regions of synaptic contact [10, 11]. In adult rodents, PNNs are composed of chondroitin sulfate proteoglycans (CSPGs) including aggrecan, versican, brevican, and phosphacan, among others; tenascin-R; hyaluronan; and link proteins such as cartilage link protein 1 = Crtl1 (Hapln1) or brain link protein 2 (Bral2) [1, 12–14]. Recent excellent reviews provide detailed information about PNN structure and function in normal development, plasticity, and disease [15, 16]. PNNs are found mainly around fast-spiking, parvalbumin (PV)-containing GABAergic interneurons within many brain regions [17–19]. However, PNNs also surround glutamatergic neurons [20–24], which can be both PV positive or negative [20, 21], and other neurons involved in fast transmission, such as glycinergic output neurons in the medial nucleus of the trapezoid body (MNTB) at the calyx of Held synapse [25, 26] and excitatory neurons in the deep cerebellar nucleus (DCN) [27–29]. Relevant to reward-related brain regions, it remains unknown whether PNNs that surround PV neurons impart similar properties as those that surround other neuronal types. Future studies using genetic methods to target PNN degradation around specific neuronal subtypes to fully address this question are needed.

PNNs appear during critical periods of development in an experience-dependent manner [30–32] and restrict plasticity in adulthood. *Wisteria floribunda* agglutinin (WFA) is most often used to label PNNs [17] that surround the soma and dendrites of PV neurons. Hence, many of the studies reviewed below examined WFA staining as a proxy for PNN plasticity (e.g., changes in intensity, number, and colocalization with other markers), which we identify in Tables 1 and 2. Removal of PNNs is most commonly accomplished by the enzyme chondroitinase ABC (Ch-ABC) derived from the bacterium *Proteus vulgaris* that digests glycosaminoglycans [33]. Ch-ABC treatment restores ocular dominance plasticity in the visual cortex of adult animals [34], enhances reversal learning in the auditory cortex [35], promotes recovery of motor learning after spinal cord injury [36] or cortical ischemia [37], and influences extinction of fear conditioning [4]. Removal of PNNs also modifies plasticity by strong stimuli: PNN removal in the hippocampus or mPFC impairs reinstatement of fear conditioning [38]. Below we review the literature showing that plasticity induced by drugs of abuse is impaired after PNN removal.

NATURAL REWARDS

Stimuli that are intrinsically rewarding (e.g., exercise, environmental enrichment, and food) dynamically alter the intensity and/or number of PNNs in numerous brain regions implicated in reward as well as in learning and memory processes (see Table 1).

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Table 1. Natural reward effects on PNNs.

Environmental enrichment (EE)	Species/Sex	Age	Brain area	Treatment	Time after treatment	Behavior	PNN result	Citation
EE: Various enrichment paradigms before and after weaning	Mice/Male & Female	PND8 and PND10	Striatum	(1) Preweaning = non-enriched, Postweaning = non-enriched (NN); (2) Pre = non-enriched, Post = enriched (NE); (3) Pre = enriched, Post = non-enriched (EN); 4) Pre = enriched, Post = enriched (EE)	PND8 and PND10 following treatment	Open field, Forced swim, and Morris water maze	Striatum-↑ in WFA density with EE at PND10	Simonetti et al., 2009
EE: 1 month exposure	Mice/Female	Adult	Deep cerebellar nuclei (DCN)	1 month of EE	Following EE exposure	–	DCN: ↓ WFA positive cells	Foscarin et al., 2011
EE: Acute (22 h) and extended (30d) exposure	Rat/Male	Adult	Prefrontal cortex (PFC): Prelimbic (PL), infralimbic (IL), orbitofrontal cortices (OFC)	22 h or 30 days of EE	Following EE exposure	Coincided with incubation of sucrose craving studies (showed incubation)	PFC-PL: ↑ in WFA intensity with acute EE and extended + sucrose training, acute EE by itself ↓ WFA intensity; IL: ↑ in WFA intensity with acute EE + sucrose training; OFC: ↑ in WFA intensity with acute EE and extended + sucrose training, acute EE by itself ↑ WFA intensity	Slaker et al., 2016
EE: Late-pregnant dams and offspring maintained in EE after weaning until euthanized (P15 or adults)	Mice/Male & Female	PND15 or Adult (12–14 wks)	Striatum: Medial and lateral	Late-pregnant dams and their offspring were maintained in either standard enrichment or EE after weaning coinciding with what what experienced by their respective dams	Following EE exposure	–	Striatum-Medial: ↑ in WFA density with EE between adult and PND15; Lateral: ↓ in WFA density with EE between adult and PND15, ↑ in WFA density with EE at PND15	O'Connor et al., 2019
Exercise	**Species/Sex**	**Age**	**Brain area**	**Treatment**	**Time after treatment**	**Behavior**	**PNN result**	**Citation**
Exercise: ad libitum access to a running wheel	Rat/Female	Adult	Cingulate cortex	6 weeks ad libitum access to a running wheel	Following exercise exposure	Running Distance	Cingulate cortex: ↓ in PNN # and thickness	Smith et al., 2015
			Hippocampus: CA1, CA3, CA3, dentate gyrus (DG)				Hippocampus-CA1: ↓ in PNN # and thickness; CA3: ↓ in PNN thickness; DG: ↓ in PNN number and thickness	
			Lateral hypothalamus				Lateral hypothalamus: ↑ in PNN #	
			Striatum: Caudate/putamen				Striatum: ↓ in PNN # and thickness	
Obesogenic diets	**Species/Sex**	**Age**	**Brain area**	**Treatment**	**Time after treatment**	**Behavior**	**PNN result**	**Citation**
Hight fat: 60.0% fat, 20.0% carbohydrates, 20.0% protein	Rat/Male	Adult (P60–80)	Prefrontal cortex (PFC): Prelimbic (PL), infralimbic (IL),	Ad libitum or calorically-matched diet exposure for 21 days	Following diet exposure	Signficant weight gain in ad libitum 60% HF fed rats	PFC-PL: ↓ in WFA intensity with 60% HF exopsure regardless of	Dingess et al., 2018

Table 1. continued

Environmental enrichment (EE)	Species/Sex	Age	Brain area	Treatment	Time after treatment	Behavior	PNN result	Citation
			orbitofrontal cortices (OFC)				weight gain; OFC: ↓ in WFA intensity and # with 60% HF exopsure regardless of weight gain	
Hight fat: 60.0% fat, 20.0% carbohydrates, 20.0% protein	Rat/Sprague-Dawley (SD) and SD selectively bred obesity prone (OP) and obesity resistant (OR)/ Male & Female	Adult (P60–80)	Prefrontal cortex (PFC): Prelimbic (PL), infralimbic (IL), orbitofrontal cortices (OFC)	Ad libitum diet exposure for 21 days	Following diet exposure	Signficant weight gain in ad libitum 60% HF fed male SD rats and female obesity prone rats	PFC-PL: ↓ in WFA intensity w/60% HF exposure in male SD and OP rats; IL: ↑ in WFA inensity w/ 60% HF exosure in female SD and OP rats, ↑ in colocalization of WFA/PV# in OP female rats w/60% HF exposure, ↓ in WFA intensity in OR female rats w/60% HF exposure; OFC: ↓ in WFA intensity and colocalization of WFA/PV# w/60% HF exopsure in SD and OP male rats, ↑ in WFA intensity in OR male rats w/60% HF exposure	Dingess et al., 2018
Hight fat: 60.0% fat, 20.0% carbohydrates, 20.0% protein	Rat/Male	Adult (8 wks)	Hypothalamus: Medial arcuate (mARH), lateral arcuate (lARH)	Ad libitum diet for 2 weeks followed by streptozotocin injection to induce type II diabetic state and monitored for another 24 days	Following treatment	Significant weight gain and blood glucose levels in model of type II diabetes	Hypothalamus-mARH: ↓ WFA intensity in HF + streptozotocin injected rats, lARH: ↓ WFA intensity in HF + streptozotocin injected rats	Alonge et al., 2020
Hight fat: 60.0% fat, 20.0% carbohydrates, 20.0% protein	Mice/Male & Female	Adult (15 wks)	Hypothalamus: Arcuate (ARH), terete (TE), paraventricular (PVH), lateral (LH), anterior (AH), ventromedial (VMH), dorsomedial (DMH), perifornical area of the anterior (PeFAH)	Ad libitum diet for 4 weeks ± sham/ gonadectomy (GDX) ± fed or fasted state	Following diet exposure or overnight after fasting	Significant weight gain in HF fed mice amongst other metabolic parameters	Hypothalamus-ARH: ↓ WFA intensity in GDX mice regardless of sex and diet; TE: Female mice (sham) have an ↑ WFA intensity compared to intact males, High fat fed female mice have ↑ WFA intensity compared to chow fed female mice when not fasted	Zhang et al., 2021
High fat and high sugar: 20% fat, 39.6%	Rat/Male	Adolescence (P28)	Prefrontal cortex (PFC): Prelimbic (PL), infralimbic (IL),	Intermitent diet exposure for 2 h/day for 28 days	Following diet exposure	Impaired social recognition memory	PFC-PL: ↑ in colocalization of PV/ WFA; IL: ↓ in WFA# (layers II/III and V/VI)	Reichelt et al., 2019

Table 1. continued

Environmental enrichment (EE)	Species/Sex	Age	Brain area	Treatment	Time after treatment	Behavior	PNN result	Citation
carbohydrates, 19.4% protein			anterior cingulate (ACC)				and an ↑ in PV/WFA colocalization in HFHS; ACC: ↑ in colocalization of PV/WFA in HFHS	
High fat and high sugar: 21.0% fat, 49.2% carbohydrates, 17.7% protein	Mice/Male	Adolescence (P26) & Adult (P68)	Hippocampus: CA1, CA2/3, Dentate gyrus (DG)	Ad libitum diet exposure for 5 week	Following diet exposure	Signficant weight gain in adolescent and adult mice	Hippocampus-CA1: ↓ in WFA# in adults fed HFHS and an ↑ in PV/WFA colocalization in adults regardless of diet; CA2/3: ↑ in PV/WFA colocalization in adults regardless of diet	Reichelt et al., 2021
			Prefrontal cortex (PFC): Prelimbic (PL), infralimbic (IL), orbitofrontal cortices (OFC)				PFC-PL: ↑ in WFA# in adults regardless of diet; IL: ↑ in WFA# and PV/WFA colocalization in adults regardless of diet	
Sucrose	**Species/Sex**	**Age**	**Brain area**	**Treatment**	**Time after treatment**	**Behavior**	**PNN result**	**Citation**
Sucrose: 10% solution	Rat/Male	Adult	Prefrontal cortex (PFC): Prelimbic (PL), infralimbic (IL), orbitofrontal cortices (OFC)	2 h/day X 10 days ± environmental enrichment	1 or 30 days	Coincided with incubation of craving studies (showed incubation)	No significant sucrose-induced effects	Slaker et al., 2016
Sucrose: pellets	Rat/Male	Adult	Prefrontal cortex (PFC): Prelimbic (PL), infralimbic (IL), orbitofrontal cortices (OFC)	2 h/day X 10 days	1 or 30 days	Coincided with incubation of craving studies (sucrose did not show incubation)	No significant sucrose-induced effects	Roura-Martinez et al., 2020

Table 2. Drug reward effects on PNNs.

Cocaine Sensitization	**Species/ sex**	**Age**	**Brain area**	**Treatment**	**Time after treatment**	**Behavior**	**PNN result**	**Citation**
Cocaine sensitization (20 mg/kg), IP	Mice/Male	Adult (8 weeks)	Cerebellum	1X/day x 6 days every 48 h	1 month + acute cocaine challenge (10 mg/kg), IP	Sensitized locomotor activity and sniffing	Medial nucleus: ↓ WFA intensity	Vazquez-Sanroman et al., 2015a
Cocaine sensitization (20 mg/kg), IP	Mice/Male	Adult (PND 77)	Cerebellum	1X/day x 6 days every 48 h	7 days + acute cocaine challenge (10 mg/kg), IP	Sensitized locomotor activity and sniffing	Medial nucleus: ↑ WFA intensity	Vazquez-Sanroman et al., 2015b
Cocaine sensitization (15 mg/kg), IP	Rats/Male	Adult	Prefrontal cortex (PFC): Prelimbic (PL) and infralimbic (IL)	1X or 5X daily	2 or 24 h	Sensitized locomotor activity	1 Day: PFC-PL and IL: ↓ WFA intensity 2 h later; IL: ↑ WFA intensity 24 h later	Slaker et al., 2018
							5 Day: PFC-PL and IL: ↑ WFA intensity 2 h later	
Conditioned place preference (CPP)	**Species/ sex**	**Age**	**Brain area**	**Treatment**	**Time after treatment**	**Behavior**	**PNN result**	**Citation**
Cocaine CPP (20 mg/kg), IP	Mice/Male	7 weeks	Cerebellum	1X/day alternating, 8 days total	1 day after preference test (2 days after last cocaine)	Subset shows CPP = Preference (PREF) group	Golgi cells: ↑ WFA intensity in PREF group; DCN cells: ↓ WFA intensity in all cocaine groups independent of preference	Carbo-Gas et al., 2017
Cocaine CPP (15 mg/kg), IP	Rats/Male	Adult	Cerebellum	1X/day alternating, 8 days total	90 min after preference test (2 days after last cocaine)	IL mPFC lidocaine infusion increased cocaine CPP	Golgi cells: ↑ WFA intensity in after IL mPFC lidocaine treatment during training days	Guarque-Chabrera et al., 2022
Cocaine CPP (12 mg/kg), IP	Rats/Male	Adult	Prefrontal cortex (PFC): Prelimbic (PL)	3X/day alternating	30 min, 2 h, 24 h	CPP	No change in WFA intensity; Decreased PV intensity at all time points	Jorgensen et al., 2020
Self-administration	**Species/ sex**	**Age**	**Brain area**	**Treatment**	**Time after treatment**	**Behavior**	**PNN result**	**Citation**
Cocaine self-administration (0.3 mg/infusion), IV	Rats/Male	Adult	Cerebellar cortex: (vermis and hemispheres)	2 h/day X 7 days; half given 1 h/day (ShA) or 6 h/day (LgA) X 20 days	1, 7, or 28 days abstinence	6 h vs 1 h access escalated cocaine intake	↑ WFA intensity with abstinence in ShA and LgA rats 1 Day	Sanchez-Hernandez et al., 2021
							↓ WFA intensity vs. naïve in ShA 28 days	
							↑ WFA intensity vs. naïve in LgA rats	
Cocaine self-administration (0.75 mg/kg/infusion), IV	Rats/Male	Adult	Prefrontal cortex (PFC): anterior cinglulate; ventral or dorsal prelimbic (v or dPL); ventral infralimbic (IL), insular, ventral orbitofrontal (vOFC), lateral orbitofrontal (lOFC)	6 h/day X 10 days	1 or 30 days abstinence	Self-administration	1 Day: PFC-dPL, vPL, IL: ↑ number of WFA cells dependent on level of WFA intensity and hemisphere 30 Days: No changes	Roura-Martinez et al., 2020
Ethanol	**Species/ sex**	**Age**	**Brain area**	**Treatment**	**Time after treatment**	**Behavior**	**PNN result**	**Citation**
Ethanol (2.5 g/kg), SC	Mice/Male & Female	PND 7	Barrel cortex	2X injection, 2 h apart at PND 7	7 days or 83 days		Barrel cortex: PND 14: ↑ number of WFA cells in L4/5; PND 90: ↑ number of WFA cells not co-labeled with PV; ↓ number of PV/ WFA cells;	Saito et al., 2019

Table 2. continued

Cocaine Sensitization	Species/ sex	Age	Brain area	Treatment	Time after treatment	Behavior	PNN result	Citation
			Hippocampus: dentate gyrus (DG)				Hippocampus-DG: PND90: ↓ number of WFA cells	
Ethanol (2.5 g/kg), SC	Mice/Male & Female	PND 7	Hippocampus: CA1/CA3	2X injection, 2 h apart at PND 7	83 days	Decreased contextual fear conditioning; Increased fragmentation of slow-wave sleep; hyperactivity	Retrosplenial cortex: ↓ number of WFA cells	Lewin et al., 2018
			Retrosplenial cortex					
Ethanol, drinking-in-the dark procedure (20% ethanol vs. water)	Mice/Male	8 weeks	Insular cortex and primary motor cortex	4 h/day xX 4 days/ week for 1 week or 6 weeks	20 h	Alcohol self-administration	Insular cortex: ↑ WFA, aggrecan, brevican, and phosphacan intensity at 6 weeks	Chen et al., 2015
Ethanol (5 g/kg, 25% ethanol)	Mice/Male	28–37 days	Prefrontal cortex: Orbitofrontal cortex (OFC)	Ethanol (intragastic) 6 days between PND 28–37	73 days	Decreased reversal learning on Barnes maze; Decreased center time in open field	PFC-OFC: ↑ WFA, brevican, and neurocan intensity	Coleman et al., 2014
Ethanol (25, 50, or 75 mM) or intragastric (5.25 g/kg)	Rats/Male	21 days	Primary cortical astrocytes or hippocampus or intragastric treatment 2X at PND 4–9	1 day	0 days		Cortical and hippocampal cultures: ↓ arylsulfatase B activity; ↑ C4S; ↑ cellular and medium neurocan mRNA and protein in cortical cultures; Hippocampus in vivo ethanol: ↑ neurocan	Zhang et al., 2014a
Ketamine	**Species/ sex**	**Age**	**Brain area**	**Treatment**	**Time after treatment**	**Behavior**	**PNN result**	**Citation**
Ketamine (30 mg/ kg), IP	Mice/Male	Not specified	Hippocampus: CA1	7 daily	1 day	Increased locomotion; decreased prepulse inhibition with low-intensity stimulus	Hippocampus-CA1 (so and sp), Basket cells: ↓Total PV + and Cat-315 + /PV + cells; Axoaxonic cells: ↓ total PV + and Cat-315-/PV + cells; O-LM/H-S* cells: ↓ total PV +, Cat-315 + /PV +, and Cat-315-/ PV +, cells; Bistratified (so): ↓ PV + and Cat-315-/PV + cells	Fujikawa et al., 2021
Ketamine (30 mg/ kg), IP	Rats/Male	Adult (8 weeks)	Prefrontal cortex (PFC)	5 daily/2 d off/5 daily/2 d/12 d isolation/2 d social interaction test	2 days	Decreased non-aggressive social interaction	PFC: ↓ number of WFA cells; no change in number of PV cells or double-labeled WFA/ PV cells	Matuszko et al., 2017
			Hippocampus: CA1				Hippocampus-CA1: No change in WFA cell number or dendrite intensity of WFA	
Ketamine (30 mg/ kg), IP	Rats/Male	Adult (8 weeks)	Prefrontal cortex (PFC)	5 daily/2 d off/5 daily/2 d/12 d isolation/2 d social interaction test	2 days		PFC: PV + cells: ↓ WFA-labeled unit area; fine structure analysis: ↑ number but smaller, less circular WFA-labeled units	Kaushik et al., 2020

Table 2. continued

Cocaine Sensitization	Species/ sex	Age	Brain area	Treatment	Time after treatment	Behavior	PNN result	Citation
Ketamine (100 mg/kg)/xylazine (10 mg/kg)/acepromazine (3 mg/kg), IP (KXA)	Mice/Male & Female	Adult (8–12 weeks)	Somatosensory cortex: S1	1X, 2X, 3X, 6X; once every 72 h	4 h	3X KXA, every 2 days; Increased ocular dominance plasticity in layer 4 of V1 after brief (3 d) monocular deprivation	S1: ↓ percent of WFA-coated cells after 2–6 injections;	Venturino et al. 2021
Nicotine	**Species/ sex**	**Age**	**Brain area**	**Treatment**	**Time after treatment**	**Behavior**	**PNN result**	**Citation**
Nicotine self-administration (0.03 mg/kg/infusion), IV	Rats/Male	Adult	Prefrontal cortex: Orbitofrontal cortex (OFC)	1 h/day X at least 21 days	45 min or 3 days	Self-administration	PFC-OFC: ↓ number of PV cells surrounded by WFA & ↓ intensity of WFA at 45 min;	Vazquez-Sanroman et al., 2016
			Ventral tegmental area (VTA)				VTA: ↓ number of PV cells surrounded by WFA at 45 min and 3 days; ↓ intensity of WFA at 45 min	
Opioids	**Species/ sex**	**Age**	**Brain area**	**Treatment**	**Time after treatment**	**Behavior**	**PNN result**	**Citation**
Heroin self-administration (100 µg/kg/infusion), IV	Rats/Male	Adult	Dorsal striatum	3 hr/day X 16 days; Extinction 1 h/day X 15 days	21 days abstinence; Extinction; Reinstatement	Self-administraition		Van den Oever et al., 2010
			Nucleus accumbens (Nac)				NAc: Extinction: ↓ tenascin-R (180 & 160 kDa); Cue reinstatement: partially restored tenascin-R	
			Prefrontal cortex (PFC)				PFC: 21 days abstinence: ↓ synaptosomal tenascin-R (160 kDa), ↓ brevican - Bcan; (145 kDa); Extinction: ↓ Bcan (145 kDa); Cue reinstatement: ↑ Bcan (145 kDa) to pre-extinction levels	
Heroin self-administration (0.075 mg/kg/infusion), IV	Rats/Male	Adult	Prefrontal cortex (PFC): Infralimbic (IL) and orbiotofrontal cortex (OFC)	6 h/day X 10 days	1 or 30 days abstinence	Self-administration	PFC- IL and OFC: 1 Day: ↑ number of WFA cells	Roura-Martinez et al., 2020
							PFC- OFC: 30 Days: ↑ number of WFA cells	

These regions include the prefrontal cortex (PFC) [39–43], striatum [44], cingulate cortex [44], hippocampus [42, 44], and hypothalamus [44–46]. Although natural rewards such as exercise can impact PNNs in areas outside those discussed above (i.e., areas of the central nervous system associated with motor control), discussion of these studies is outside the scope of this review, which is focused primarily on the interplay between PNNs and the circuitry involved in reward after exposure to reinforcing stimuli (see Table 1 for a summary of the findings).

Impact of food on PNNs

Growing evidence suggests that diet, particularly the Western diet (rich in saturated fats and refined sugars), influences the expression and intensity of PNNs [41, 42]. This diet may functionally impact the neurons they surround, altering the protective microenvironment PNNs provide [47–51] and impacting synaptic stabilization [49, 52]. Numerous reviews have also discussed the detrimental impact obesogenic diets have on neuroplasticity [53], neuroinflammation [54, 55], neuropsychiatric disorders [54], neurodegenerative and neurodevelopmental diseases [56], cognition [57], and the overall harmful effects obesity and obesogenic diets have on the brain [58]. Given the overlap between PNNs and the pathophysiological impact obesogenic diets have on the brain, understanding how diet influences the maturation and maintenance of PNNs may provide valuable insights into mechanisms that influence overconsumption of unhealthy foods that promote obesity.

Obesogenic diets

Foods that are high in saturated fat and refined sugars are prevalent and play a key role in overeating, weight gain, and obesity globally [59, 60]. The detrimental impact of these unhealthy diets on brain physiology and function is becoming evident [58]. Here we examine the impact obesogenic diets have on PNNs within the reward circuitry which may contribute to altered neuronal communication and promote maladaptive food-seeking behaviors.

Exposure to ad libitum 60% high fat diet in adult male rats for 3 weeks decreases PNN intensity in the prelimbic PFC and orbitofrontal cortex (OFC) regardless of weight gain [39]. Furthermore, when male rats selectively bred to be obesity prone or obesity resistant were exposed to the same dietary conditions, obesity prone rats showed decreases in PNN intensity similar to Sprague-Dawley outbred rats [40]. On the other hand, PNNs from obesity resistant rats had the opposite response to high fat diet, with an increase in PNN intensity in the OFC, indicating that genetic predisposition towards obesity may impact high fat-induced adaptations independent of weight gain. This is particularly intriguing as it suggests that other factors that distinguish obesity prone from obesity resistant rats, such as reward processing/perception, may be impacting PNNs to influence food-seeking behavior [61, 62].

In addition to examining the impact of diet on males, Dingess et al. [40] provided one of the few studies that conducted a comparative examination of diet on female rats in the PFC. The authors report that, unlike males, females had an increase in PNN intensity in the infralimbic region of the PFC, which was observed in both Sprague-Dawley and selectively bred obesity prone rats. In contrast, PNNs from obesity resistant females had decreased PNN intensity. However, unlike PNNs from males, we cannot conclude that the changes in PNNs are independent of weight gain, as the authors did not examine this in females [40].

Although the studies discussed above suggest that dietary high fat significantly alters PNN intensity, other studies suggest that the influence of diet is not so straightforward. Reichelt et al. [42] recently showed that male mice fed a diet high in fat (21%) and high in sugar (49%) for 5 weeks did not impact PNNs in the PFC. However, the same authors showed that intermittent exposure to the same diet for 28 days in male rats decreased the number of PNN-labeled cells in the infralimbic region of the PFC and increased colocalization of PV and PNN neurons in the prelimbic, infralimbic, and anterior cingulate regions of the PFC [41]. In addition, unpublished data by Dr. Brown's lab showed a decrease in PNN intensity in males within the infralimbic region of the PFC after exposure to "junk-food" (mash of Ruffles potato chips (40 g), Chips Ahoy chocolate chip cookies (130 g), Jif smooth peanut butter (130 g), Nesquick powdered chocolate flavoring (130 g), powdered Lab Diet 5001 (220 g) [63]), which aligns with what has been found in the high-fat and high-sugar diets. Taken together, these findings suggest that there is a complex interplay between age, diet formulations, sex, genetic predisposition, and administration protocols that impacts PNNs within the PFC.

The role of PNNs in hippocampal plasticity has been well documented (for reviews refer to [16, 52]). However, few studies have examined the impact rewarding stimuli have on PNNs within the hippocampus. In addition to examining the PFC (discussed above) Reichelt et al. [42] showed that 5 weeks of exposure to a diet high in fat and sugar reduced the number of PNN positive cells in the CA1 subregion of the hippocampus in adult but not adolescent male mice, which correlated with adiposity [42]. The authors speculated that the CA1 subregion of the hippocampus may be more vulnerable to nutritional stress in adults, and that younger brains may have some resilience to diet-induced dysregulation, as PNNs are not fully mature.

The lateral hypothalamus plays a critical role in motivated behaviors and sends projections to the ventral tegmental area that are important for driving goal-oriented activities [64]. Rats exposed to dietary high fat in conjunction with type II diabetes have reduced PNN intensity in the arcuate nucleus of the hypothalamus [45]. However, Zhang et al. [46] showed that sex hormones impacted PNN intensity in the arcuate regardless of diet exposure in mice, suggesting an interplay between PNNs and metabolic dysfunction independent of diet. Additional evidence that metabolic dysfunction impacts PNNs has been observed in *ob/ob* mice, which show attenuated PNN immunoreactivity in the median eminence and failure to dynamically respond to food challenges [65]. Finally, ad libitum consumption of 60% high fat diet induces sex specific changes in PNN intensity (increase) in the terete nuclei of the hypothalamus in non-fasted female mice. Hence, numerous factors such as nutritional regulation, fasting state, metabolic dysfunction, and sex, can impact PNNs within the hypothalamus. Future studies will need to delineate the role PNNs play in hedonic vs. homeostatic feeding within the hypothalamus.

Sucrose

Data suggests that consumption of sugars and the development of obesity is a problem when sugar consumption results in excess caloric intake, and not because of sugar directly [66]. Sucrose consumption can modify neuronal characteristics similarly to those found after exposure to drugs of abuse within the reward circuit, distorting motivation towards an "addictive" phenotype [67]. Although dietary high fat and sucrose both alter dendritic spine morphology ([68–70] structural indicators of glutamatergic plasticity) in the PFC, there has been no evidence to date that sucrose causes adaptations to PNNs as does high fat.

Studies conducted by Slaker et al. [43] and Roura-Martinez et al. [71] found that 1 day or 30 days after sucrose consumption either 10% sucrose solution or sucrose pellets, respectively, resulted in no significant alterations in PNNs in the PFC. This is particularly intriguing given the evidence that high fat and combinations of high fat and high sugar can modify PNNs within the PFC. Hence, future studies need to determine the molecular changes that macronutrients may trigger to modify PNNs.

Exercise

Exercise has been shown to be rewarding, and inactivation of either the PFC or nucleus accumbens can diminish the rewarding

aspects of exercise [72]. Smith et al. [44] showed that ad libitum access to a running wheel for 6 weeks influenced PNNs within numerous brain regions. Specifically, there was a decrease in PNN number and thickness in the striatum, cingulate cortex, and hippocampus, but an increase in PNN number in the lateral hypothalamus. Physical activity has been shown to be beneficial for health and alleviating a myriad of diseases, including drug addiction and obesity [73, 74]. Based on what little evidence we have for exercise-induced changes in PNNs and the beneficial consequences of exercise on physiological and pathophysiological processes that PNNs also respond to, it is surprising more research has not been carried out examining how PNNs in the brain respond to exercise, while several studies have examined the impact of exercise on PNNs in the spinal cord, typically after a spinal cord injury [44, 75–77].

Environmental enrichment

Environmental enrichment promotes behaviors that animals find rewarding, improves recovery from brain injury, and enhances learning and memory [78]. In addition, environmental enrichment diminishes the effects of chronic stress [79] and decreases the rewarding effects of drugs of abuse [80–88] and sucrose [89–91]. PNN plasticity is affected by environmental enrichment in several brain areas including, but not limited to, the striatum [92, 93], deep cerebellar nuclei [94], and PFC [43] (see Table 1). However, to date, only one study has examined the interaction between environmental enrichment and reward seeking on PNN changes. Slaker et al. [43] found that acute environmental enrichment (22 h) reduced PNN intensity in the prelimbic region of the PFC and increased PNN intensity in the OFC. There was no direct effect of extended (30 d) environmental enrichment on PNNs. However, when environmental enrichment was combined with sucrose self-administration training, there was a synergistic effect, as PNN intensity was increased within the prelimbic PFC in rats that were exposed to either acute or extended environmental enrichment combined with sucrose training. This effect was not seen in animals that were exposed to sucrose self-administration or environmental enrichment independently. Similar synergy was found in the infralimbic and OFC PFC regions (see Table 1). These data are intriguing considering the lack of evidence showing an effect of sucrose on PNNs. Further studies need to determine whether environmental enrichment triggers sucrose-induced PNN-associated plasticity, which is normally absent, or whether the experience of sucrose adds something to the augmented experience of environmental enrichment itself.

DRUGS OF ABUSE

Several studies have shown that drugs of abuse either decrease or increase the number and/or intensity of PNNs (see [95] for review). Different classes of drugs, including ethanol, nicotine, cocaine, ketamine, and heroin, alter the intensity or number of PNNs in various brain regions, including the mPFC [96–99], anterior cingulate cortex [100], OFC [101], barrel cortex [102, 103], insula [104], hypothalamus [105, 106], hippocampus [102, 107] ventral tegmental area [101], and cerebellum [24, 108–110] (see Table 2 for a summary of the findings).

Cocaine

Most studies examining drugs of abuse focused on how cocaine exposure altered PNNs, and most of these tested the effects of cocaine on PNNs in the mPFC and the cerebellum. Investigator-administered cocaine includes studies examining locomotor sensitization or conditioned place preference (CPP), while self-administration studies incorporate the commonly used 2 h or 6 h daily training sessions.

In the prelimbic PFC, investigator-administered cocaine decreased PNN intensity after an acute cocaine injection, but increased intensity after repeated cocaine [96], which induced locomotor sensitization. Cocaine-induced CPP studies have not shown changes in PNN intensity or number of PNNs upon retrieval of the cocaine-associated CPP memory [111]. The divergences may have been due to different timing of the cocaine injections, five daily injections for the sensitization studies and three cocaine injections (48 h apart) in the CPP study, as PNNs were assessed 2 h and 24 h after treatment in both studies. These findings are opposite to what was found in cocaine self-administering rats in which the number of PNNs was increased in the prelimbic PFC after 1 day but not after 30 days of abstinence from cocaine, although here the increase was dependent on the intensity and hemisphere in which PNNs were assessed [71]. Most of the studies discussed above compared sucrose to cocaine to delineate drug-induced changes from changes associated with natural rewards (Fig. 1).

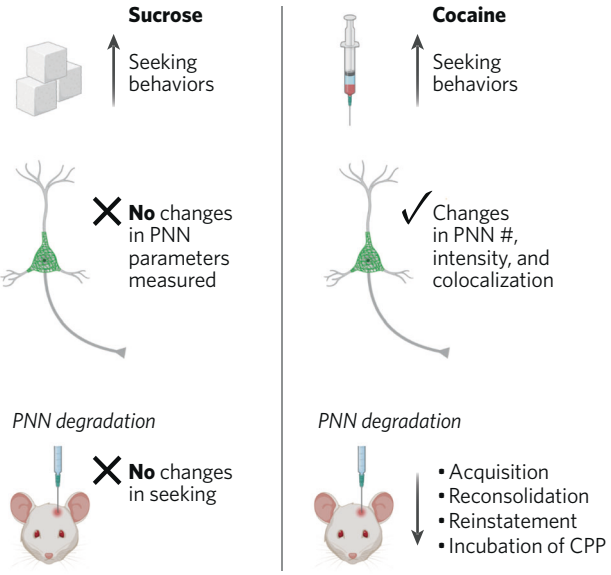

Fig. 1 Comparison of the effects of sucrose and cocaine on PNNs and the role of PNNs in seeking behaviors. Both sucrose and cocaine can facilitate motivated seeking behaviors. However, cocaine exposure and associated learning alters PNNs, and PNN degradation disrupts cocaine-seeking behaviors. To date, a role for PNN degradation in sucrose-seeking behaviors has not been observed.

In the cerebellum, repeated cocaine exposure increased the intensity of PNNs around neurons in the medial nucleus when examined after a 1-week abstinence period followed by an acute cocaine challenge [24], but the same cocaine challenge decreased the intensity around the same type of neurons when given after a 1-month abstinence period [108], suggesting that abstinence alone may induce further plasticity in cerebellar output neurons. Training for cocaine-induced conditioned place preference (CPP) increased PNN intensity in Golgi inhibitory interneurons in the cerebellum only in rats that showed place preference, while PNN intensity was decreased in medial deep cerebellar nucleus neurons independent of their place preference [110], together suggesting that Golgi neuron PNNs play a role in promoting cocaine-associated learning. The cerebellum has indirect functional connections to the PFC [97, 112], and a recent study showed that inactivation of the infralimbic but not prelimbic PFC, enhanced PNN expression around cerebellar Golgi interneurons [113]. For this latter study, animals were trained for CPP using odor cues paired with cocaine and a particular compartment but, on the preference test day, odors were presented in the opposite compartment in the absence of cocaine. Thus, it is likely that any preference exhibited was due to the conditioned odor cue rather than the contextual cue.

Cocaine self-administration studies show similar findings over abstinence time from short- (1 h) or long (6 h)- access to cocaine: in general, PNN intensity was decreased in Golgi interneurons in the cerebellar cortex at 1 day of abstinence in the short-access cocaine group, but was increased at 28 days of abstinence in the long-access cocaine group [109]. This increase in PNN intensity may therefore be associated with the "incubation" effect, which is the enhancement in drug-seeking behavior after long-term (2–4 weeks) of abstinence [114].

Ethanol

In general, ethanol exposure increases PNNs and PNN components (see [115] for review). Zhang et al. [116] showed that exposure of rat cortical or hippocampal cultures to ethanol increased sulfated forms of GAGs, neurocan, and C4S, the most prominent CS in PNNs during adulthood and a major CS associated with inhibition of axon growth [15]. These changes were accompanied by a decrease in arylsulfatase B, which removes sulfate groups from C4S, and by decreased neurite outgrowth during development. They showed similar changes in the hippocampus after in vivo exposure at PND 4–9. Another study that examined ethanol exposure early in development [117] used an adolescent binge model of ethanol exposure via intermittent intragastic administration for 6 days and reported an increase in the staining density of PNNs as well as their components, brevican and neurocan, in the OFC. These increases may be functionally related to the impairment of reversal learning, which is in part dependent on the OFC [118]. Using a different model of binge drinking (drinking in the dark procedure), Chen and Lasek [104] found similar increases in intensity staining of PNNs as well as in PNN components, including aggrecan, brevican, and phosphacan in the insular cortex 1 day after 6 weeks (but not after 1 week) of drinking bouts. These effects were not found in the primary motor cortex. In contrast to the increases found in PNNs or their components, one study showed that a double injection of ethanol to mice at PND 7 decreased the number of PNNs and PV cells in the retrosplenial cortex and CA3 region when examined in adulthood 3 months later [119]. The differences may be due to the long abstinence time. However, a follow-up study by this same group [102] found that ethanol administered at PND 7 increased the number of PNNs at PND 14 and PND 90 in the barrel cortex but decreased the number of PNNs in the dentate gyrus, suggesting region-specific effects by the same treatment and abstinence time. The number of PV cells surrounded by PNNs was decreased, suggesting a profound decrease in PV to non-detectable levels in PNN-surrounded cells or the potential loss of PV cells that were originally surrounded by PNNs.

Ketamine

Ketamine studies have largely focused on the impact of ketamine on PNNs or of removing PNNs in the context of alleviating depression or mimicking schizophrenia-like behaviors in animal models. Several studies examined the impact of ketamine in rodent models of schizophrenia. Matuskzko et al. [98] delivered daily ketamine (30 mg/kg, ip) to rats for 5 days, with a 2-day interval followed by another 5 daily injections. After 12 days of isolation housing, rats were given a social interaction test. In the mPFC, ketamine decreased the number of PNNs and PNN/PV-labeled cells, with no changes in the CA1. In a follow-up study, Kaushik et al. [99] developed a novel 2D and 3D analysis for PNN changes after repeated ketamine to assess the intensity, size, and shape of holes in mPFC PNNs. Ketamine altered several parameters in PNNs and their underlying PV neurons, including a decrease in PNN unit area and an increase in the number but smaller, less circular PNN units. Fujikawa et al. [107] identified four subtypes of PV neurons based on morphology and assessed in PV single or double-labeling using the Cat-315 antibody, which binds to aggrecan-containing PNNs with the human natural killer-1 (HNK-1) glycan [120]. In the CA1, daily ketamine decreased the number of some PV subtypes that was dependent on the presence of Cat-315 labeling, suggesting specificity of ketamine-induced plasticity within this brain region. An intriguing recent study by Venturino et al. [103] showed that as few as three anesthetic doses of ketamine given every few days profoundly depleted the number of PNNs in the barrel cortex and promoted ocular dominance plasticity after monocular deprivation. This PNN decrease was associated with activated microglia and was prevented by pharmacological depletion of microglia.

Nicotine

Only a single study has examined the impact of nicotine on PNNs. Vazquez-Sanroma et al. [101] reported decreased numbers of PV neurons surrounded by PNNs in the VTA just after the last self-administration session and at 3 days abstinence. Decreased PNN intensity was also found at the early time point, and the authors suggested that any accompanying changes in PV cell function might lead to disinhibition of burst firing of VTA dopamine neurons [121]. Nicotine self-administration also reduced PNN intensity and number of PV neurons surrounded by PNNs, but only immediately after discontinuing nicotine exposure. Unlike for cocaine and opioids, no changes in PNNs were found in the mPFC.

Opioids

Two studies have tested the impact of heroin self-administration on PNNs or PNN components. An earlier study showed that 21 days of abstinence from heroin self-administration in rats decreased synaptosomal tenascin-R (TnR) and brevican (Bcan) in the mPFC, (infralimbic and prelimbic PFC combined), while extinction over a 2-week period reduced Bcan, and remarkably, that a 30 min cue reinstatement increased Bcan back to pre-extinction levels. The latter finding suggests that rapid effects of environmental stimuli impact proteins such as Bcan that regulates localization of potassium channels and AMPAR trafficking on PV interneurons [122]. In another study, heroin self-administration increased the number of PNNs in the infralimbic PFC at 1 day of abstinence; this effect was absent by 30 days of abstinence [71]. These time-dependent effects were region-specific, since the same study demonstrated that heroin self-administration increased the number of PNNs in the ventral OFC on both 1 and 30 days of abstinence. Together, these studies are consistent with the idea that both abstinence and extinction can produce longer-term changes that may set the stage for drug- or drug-associated rapid changes in PNNs or their components.

BIOLOGICAL FACTORS THAT MAY INFLUENCE PNNS

The differential cocaine vs. sucrose findings are consistent with different neural ensembles mediating food or sucrose vs. cocaine seeking [123–125] and studies showing that treatments block reinstatement of cocaine seeking but not sucrose seeking [106, 126]. A key gap in determining why there is divergence in PNN regulation between non-drug and drug-rewarding stimuli is that little is known about what biological factors can trigger PNN plasticity. Although we speculate there is a wide range of factors, one such biological factor that may differentially trigger PNN plasticity is dopamine. For decades, the field has known that dopamine is central to the reinforcing properties of natural rewards and drugs; dopamine reinforces the consumption of drugs and moderates the salience of cues linked to the drug experience [127]. Dopamine increases the excitability of fast-spiking interneurons in the prefrontal cortex, which are primarily surrounded by PNNs and underlie the fidelity of gamma oscillations [128, 129]. In addition, dopamine promotes high-frequency cortical synchrony in anterior cingulate cortical slices, which can be enhanced by PNN degradation [100]. Furthermore,

D1-type dopamine receptor stimulation induces proteolysis of brevican and aggrecan in the rat PFC, major constituents of PNNs [130]. However, it is unclear if there is a direct relationship between the rewarding effects of dopamine and PNNs. One could argue that if dopamine was playing a direct role on PNN plasticity, we would predict similar changes between drugs and natural rewards, which has not been the case. However, dopamine concentrations are greater in response to drug-rewarding stimuli vs. biological stimuli [131, 132] and thus complicate this prediction. Degradation of PNNs with Ch-ABC in the thalamic reticular nucleus [133] or in the ventral hippocampus [134] alters the control of dopamine activity in the ventral tegmental area. Future studies need to determine to what extent dopamine levels contribute to PNN changes. Changes in PNNs may be reflective of adaptations in combination with or independent from synaptic connectivity, and may reflect the protective role PNNs play against reactive oxygen species [47], which may be generated due to excess dopamine generation after exposure to rewarding stimuli [135, 136]. Hence, future studies will need to determine if dopamine is necessary for the changes in PNNs reviewed above and what the mechanistic trigger is for dopamine-induced PNN plasticity. The changes identified above may be entirely independent of dopamine and reflective of adaptations in glutamatergic signaling or other biological triggers seen during 'critical periods' of development [137–141].

Some natural and drug rewards alter the intensity of PNN-surrounded neurons, while other rewards alter the number of PNN-surrounded neurons, and some stimuli alter both parameters. Presumably, changes in intensity provide a more nuanced way to dynamically alter plasticity-related events, such as new synaptic inputs and/or intrinsic properties of the underlying neurons that change responsiveness to incoming stimuli. A recent study has shown that the extracellular matrix component tenascin-R and Crtl1 are endocytosed and subsequently recycled in an activity-dependent manner [142]. It is intriguing to speculate that dopamine or other neurotransmitters may generate changes in intensity or number of PNNs via enhanced recycling of PNN components. The significance of this recycling pathway is not known, but in addition to sparing the need for de novo synthesis of PNN components, the recycling of components may afford the rapid ability to change several properties of their underlying neurons, such as membrane capacitance [143], ionotropic receptors, or synaptic inputs [122], which collectively alter responses to incoming stimuli.

Impact of PNN degradation on behavior

Above we have characterized the impact of both natural rewards and drugs of abuse on PNN number, thickness, and intensity. To further understand the role PNNs play in motivated behaviors, a few studies have examined the impact of pharmacologically removing PNNs on reward-seeking behaviors (Table 3).

Natural rewards

A half dozen studies to date have examined whether PNN degradation via Ch-ABC impacts the motivation to seek food, primarily sucrose [105, 106, 144, 145]. When 2-bottle choice (for ethanol), CPP, or self-administration was examined, there was no impact on sucrose-seeking behaviors. However, when ad libtum consumption of food was assessed after Ch-ABC infusion into the median eminence of the hypothalamus, there was an increase in cumulative food intake and weight gain [65]. Hence, although current evidence does not suggest a role for PNNs in motivated sucrose-seeking behaviors, it does suggest that there may be a role in consumption of some food types. This is not surprising, as there is a lack of evidence showing sucrose-induced effects on PNN plasticity, but future studies need to assess whether this lack of effect is specific to sucrose, motivated seeking for food in general, or a combination of both.

Drug rewards

Studies attempting to disrupt drug-seeking behaviors using Ch-ABC have generally found reduced responding to drugs or drug-associated cues. Removal of PNNs in the mPFC disrupted the acquisition and reconsolidation of cocaine CPP [146] and incubation of craving using a CPP paradigm [147]. PNN degradation in the hypothalamus prevented the acquisition of CPP [105] and blocked the acquisition and cue-induced reinstatement of cocaine self-administration [105, 106]. Finally, Ch-ABC infusion into the amygdala decreased cocaine-primed reinstatement in both CPP and self-administration models [145].

In addition to cocaine, Ch-ABC degradation of PNNs in the amygdala also reduced morphine-primed reinstatement of CPP and decreased heroin-primed reinstatement in a self-administration model [145]. Infusion of Ch-ABC into the insular cortex increased sensitivity to quinine-induced aversion to ethanol [144]. Therefore, disrupting PNN stability in numerous brain areas has been successful at reducing drug-seeking behaviors. Additional work is needed to determine whether this is specific to drugs, which may provide key insights into determining what physiological mechanisms trigger PNN plasticity.

Implications for PNNs on PV cell and circuit function

Most PNNs surround PV neurons (although there are several exceptions; see Introduction). As such, natural or drug reward-induced changes in PNNs can alter the firing properties of these neurons through several mechanisms that alter excitatory: inhibitory balance [148, 149]. These include the ability of PNNs to reduce membrane capacitance [143] and provide cation buffering capacity [150, 151]. PNNs or their component, brevican, also controls plasticity through glutamate receptors and specific potassium channels [122, 152]. The presence of PNNs or specific components also likely regulates synaptic inputs [122, 153], which in part may occur through the binding of PNNs to chemorepellents such as semaphorin 3 A [154].

In addition to changes in PNN-surrounded neurons themselves, reward-associated behaviors rely on the connectivity of several brain areas [155–159]. Therefore, it is important to consider how changes in PNNs could alter coordination of this circuitry. The mPFC and nucleus accumbens (NAc) are two major pathways in reward-seeking behavior [155, 158, 159]. In most, but not all brain regions, PNNs are found around PV neurons to allow for their fast-spiking nature [15, 26, 143, 160]. PV neurons are critical players in regulating the output of pyramidal neuron activity in the mPFC to the nucleus accumbens [161, 162] through their dense perisomatic connections to pyramidal neurons [163] and feedforward inhibition [164]. PV neurons are believed to communicate through precisely timed brain oscillations that synchronize neural activity. For example, PV neurons synchronize the output of pyramidal neurons into discrete groups of activated neurons thought to represent coding of separate memories [165, 166]; (see Fig. 2). Therefore, since PV neurons are essential for generating oscillations [167–170], the impact of PNNs on reward-associated behaviors is likely to be tightly linked to their influence on the PV neuron network. Gamma oscillations (30–120 Hz) are required for attention [171, 172], adapting new strategies [173, 174], and encoding reward outcomes [175] or expected outcomes [176]. PV neurons also contribute to theta oscillations (4–12 Hz) driven by cortical pyramidal neurons [170], and are thereby able to coordinate long-range communication within and across other brain regions through coupling of theta and gamma oscillations [177]. Removal of PNNs alters several properties of PV neurons [160] and increases the variability of spiking [149]. In support of the importance of normal PV function in excitatory:inhibitory balance, direct inhibition of PV neurons induces network instability [178, 179]. Thus, in the absence of PNNs or in instances where PNNs have been altered by palatable food or drugs of abuse, PV cells and pyramidal cells may not be well timed, or

Table 3. Impact of PNN attenuation on reward seeking.

Natural reward	Species/Sex	Age	Brain area	Treatment	Time relative to treatment	Behavior	Citation
Food: consumption	Mice/Male	Adult	Hypothalamus: median eminence	Ch-ABC injection and then monitored food intake	Food intake monitored for 6 days after Ch-ABC injection	↑ in cumulative food intake and weight gain	Kohnke et al., 2021
Food: CPP	Rats/Male	Adult	Amygdala: basolateral, central	Ch-ABC after food CPP training; Prior to morphine CPP extinction	12 days	No effect on acquired food CPP	Xue et al., 2014
Sucrose: 2 bottle choice	Mice/Male	Adult	Insular cortex	Ch-ABC prior to 2-bottle choice (sucrose, water)	3 days	No change	Chen and Lasek, 2020
Sucrose: CPP	Rats/Male	Adult	Hypothalamus: anterior dorsal lateral hypothalamus	Ch-ABC prior to CPP training	3 days before training for CPP	No effect on acquisition of CPP or self-administration	Blacktop et al. 2017
Sucrose: self-administration	Rats/Male	Adult	Hypothalamus: anterior dorsal lateral hypothalamus	Prior to self-administration training	1 day before training for self-administration	No effect on acquisition of CPP or self-administration	Blacktop et al. 2017
Sucrose: self-administration	Rats/Male	Adult	Hypothalamus: anterior dorsal lateral hypothalamus	Ch-ABC prior to cue reinstatement	16 h	Trend towards reduced cue reinstatement	Blacktop and Sorg, 2019
Drug reward	**Species/Sex**	**Age**	**Brain area**	**Treatment**	**Time after treatment**	**Behavior**	**Citation**
Cocaine							
Cocaine: CPP (12 mg/kg train, 10 mg/kg test), IP	Rats/Male	Adult	Prefrontal cortex (PFC): Prelimbic	Ch-ABC prior to CPP training; Prior to extinction of CPP; Prior to memory retrieval	3 days before acquisition; 1 day before extinction; 3 days before memory retrieval	Acquisition: ↓ Reconsolidation: ↓	Slaker et al., 2015
Cocaine: CPP (5 mg/kg train)	Mice/Male	Adult	Prefrontal cortex (PFC): Prelimbic Hippocampus: Dorsal	Brevican KO heterozygous		1 day: No change; 21 days: ↓ incubation of CPP; rescued by brevican expression in dorsal hippocampus but not mPFC	Lubbers et al., 2016
Cocaine: CPP (10 mg/kg train), IP	Rats/Male	Adult	Hypothalamus: Anterior dorsal lateral	Ch-ABC prior to CPP	3 days	Acquisition: ↓	Blacktop et al. 2017
Cocaine: CPP (10 mg/kg train, 5 mg/kg test), IP	Rats/Male	Adult	Amygdala: Basolateral amygdala (BLA) and central amygdala (CeA)	Ch-ABC prior to extinction of CPP	12 days	Cocaine-primed reinstatement: ↓	Xue et al., 2014
Cocaine: self-administration (0.75 mg/kg/infusion train) IV; (5 mg/kg reinstatement), IP	Rats/Male	Adult	Amygdala: Basolateral amygdala (BLA) and central amygdala (CeA)	Ch-ABC prior to extinction of CPP	15 days	Cocaine-primed reinstatement: ↓	Xue et al., 2014
Cocaine: self-administration (0.125 mg/kg/infusion), IV	Rats/Male	Adult	Hypothalamus: Anterior dorsal lateral	Ch-ABC prior to training	1 day	Acquisition: ↓ Cue-induced reinstatement: ↓	Blacktop et al. 2017
Cocaine: self-administration (0.5 mg/kg/infusion), IV	Rats/Male	Adult	Hypothalamus: Anterior dorsal lateral	Ch-ABC prior to cue reinstatement	16 h	Cue-induced reinstatement: ↓	Blacktop and Sorg, 2019
Ethanol	Species/Sex	Age	Brain area	Treatment	Time after treatment	Behavior	Citation

Table 3. continued

Natural reward	Species/Sex	Age	Brain area	Treatment	Time relative to treatment	Behavior	Citation
Ethanol 2-bottle choice	Mice/Male	8 weeks	Insular cortex Motor cortex	Ch-ABC prior to 2-bottle choice drinking over 24 h	3 days	Insular cortex: ↑ sensitivity to quinine-induced aversion to EtOH	Chen and Lasek, 2020
OPIOIDS	**Species/Sex**	**Age**	**Brain area**	**Treatment**	**Time after treatment**	**Behavior**	**Citation**
Morphine CPP (10 mg/kg train, 30 mg/kg test), SC	Rats/Male	Adult	Amygdala: Basolateral amygdala (BLA) and central amygdala (CeA)	Ch-ABC prior to extinction of CPP	12 days (reinstatement); 10 days (retention); 4 days (reconsolidation)	Morphine-primed reinstatement of CPP: ↓ No effect on retrieval, reconsolidation, or retention	Xue et al., 2014
Heroin self-administration (0.05 mg/kg/infusion train) IV; 0.25 mg/kg reinstatement) SC	Rats/Male	Adult	Amygdala: Basolateral amygdala (BLA) and central amygdala (CeA)	Ch-ABC prior to extinction of CPP	13 days (reinstatement); 40 days (spontaneous recovery)	Heroin-primed reinstatement of self-administration: ↓ Spontaneous recovery: ↓	Xue et al., 2014

phase-locked, to theta or gamma rhythms [160], which could perturb behavioral output, including drug-associated memories that are thought to drive relapse. We speculate that dynamic changes in PNNs may optimize in a layer-specific manner low- and high-frequency inputs differently within distinct circuits to drive food- and drug-seeking behaviors. Altered PNN composition, intensity, or density, is expected to change PV neuronal function and in turn degrade the normally precise spatiotemporal firing patterns. This variability in firing patterns may produce overlapping neuronal ensembles, leading to less specificity of which ensembles represent a particular stimulus or memory [179, 180] (Fig. 2). Thus, on the one hand, by virtue of their ability to optimize and maintain the precise firing of PV neurons, PNNs appear to stabilize the network, and any food- or drug-induced alterations in PNNs within one brain region may manifest as impaired coupling of communication across many brain regions and disrupt desirable behaviors such as high-level cognition and decision making. On the other hand, too much rigid stabilization of a network in response to repeated exposure to drugs of abuse or highly palatable food may manifest as deeply entrenched and undesirable reward-related behaviors, and temporary degradation of PNNs might allow for the plasticity needed to render newer, healthy behaviors to replace drug-related behaviors.

Limitations

Most of the studies we reviewed analyzed how WFA staining was modified after exposure to a rewarding stimulus, which can provide an indirect measure of PNN plasticity by measuring one of three parameters: (1) WFA intensity; (2) WFA number; and (3) WFA colocalization. WFA intensity is often used as a proxy for determining the maturity of the PNNs, with immature PNNs labeled with less WFA stain [181]. One problem comparing between studies with respect to intensity is the diverse way which intensity is quantified. That is, some studies use semi-quantitative measures and others average a set number of pixels within a given PNN. Work by Slaker et al. has decreased the variability in quantified WFA intensity measures using a "region of interest" strategy in conjunction with automated software, PIPSQUEAK [181]. The authors make a compelling argument for less biased data, which is reproducible and able to speed up analysis by 100-fold. Future studies need to use additional techniques, such as high- and super-resolution imaging to identify the fine structure of PNNs and changes after stimulation [99, 182] by natural and drug rewards to verify what is causing the alterations in WFA staining to better understand the specific modifications within PNNs.

CONCLUSIONS

Overall, the pattern of changes in PNNs after exposure to natural rewards and drugs of abuse is highly variable and dependent on brain area, drug dose and class, sex, genetic predisposition, and exposure duration. Some studies show that short-term abstinence from drugs of abuse reduces PNNs, whereas long-term abstinence increases PNNs or vice-versa, but one conclusion that can be drawn from these studies is that PNNs are dynamic and either or both exposure time and abstinence time change PNNs in opposing directions. Reward-induced changes in PNN numbers or intensity are expected to modulate the function of their underlying neurons. Removal of PNNs most consistently reduces the firing rate of fast-spiking PV neurons [160] by imposing changes in intrinsic and synaptic properties. These changes in firing pattern are likely to interfere with the exquisite timing of coordinated output needed to stabilize the network that may support drug-related behaviors.

Future research directions

Several fundamental questions remain regarding PNN regulation. Perhaps the greatest challenge facing the field currently is that

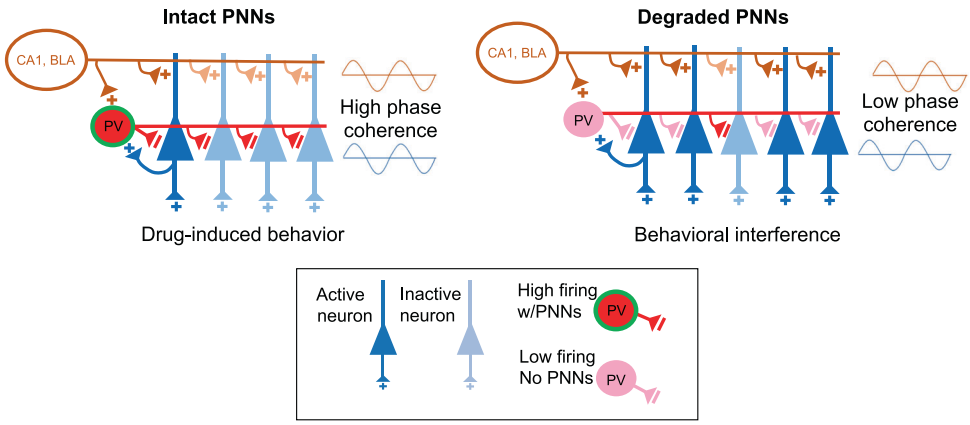

Fig. 2 Model for how PNN removal interferes with drug-induced behaviors. PNN removal in the mPFC may alter activity of neural ensembles that form memories to drive relapse behavior. With intact PNNs, glutamatergic signaling from regions such as the BLA or CA1 increase activity of both pyramidal and PV neurons. PV neurons are activated slightly after pyramidal neurons to provide feedforward inhibition on pyramidal neurons to silence and reduce the competition from nearby pyramidal neurons. In this way, PV neurons synchronize output so that only discrete neural assemblies, groups of neurons activated and linked spatially and temporally to provide information, are activated [186]. PNN removal reduces PV cell firing and provides less inhibition to pyramidal neurons, causing overlap and thus interference with neurons representing the original drug memory [179, 180]. Thus, although excess pyramidal neuron activity may enhance plasticity, the consequence may be decreased coherence across brain regions, which interferes with drug-associated memories.

numerous studies have characterized observational changes in PNNs, but little is known about the physiological mechanisms that trigger PNN plasticity and what adaptations within the PNNs account for the alterations in WFA staining. The field needs a better understanding of the relationship between PNNs and other molecules (e.g., PV and activity-dependent proteins), which may influence PNNs and vice versa. Once we have a better understanding of the physiological mechanisms triggering PNN plasticity, future studies will be able to address how physiological changes in PNNs by food/drugs of abuse impact local and downstream neural circuits to alter motivated behaviors. Another understudied area with respect to PNNs and reward circuity are sex differences. Several biological mechanisms (i.e., pharmacokinetics, neurotransmission, and hormones such as estrogen) differ between males and females and have been shown to influence drug sensitivity in almost all phases of substance use disorder (see [183, 184] for a comprehensive review on the influence of sex on drug abuse). Furthermore, sex differences have been reported for natural rewards [141, 185]. However, only two studies reported sex differences in PNNs and both reported region-specific differences [40, 46]. Hence, future studies need to consider sex differences when drawing conclusions about reward-triggered changes in PNNs. Finally, it is apparent that not all rewarding stimuli trigger PNN plasticity to the same degree and within the same brain regions. For instance, the studies reviewed above suggest sucrose by itself does not impact PNNs. However, sucrose in combination with other macronutrients (i.e., high fat) or environmental enrichment does seem to trigger PNNs plasticity. We need a better foundational understanding of what physiological mechanisms trigger PNN adaptations and the mechanisms by which PNNs maintain stability of the network. This level of understanding is expected to provide opportunities for innovative solutions to disrupt excessively stable drug-associated networks that are thought to underlie long-enduring drug behaviors.

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