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# Addiction in focus: molecular mechanisms, model systems, circuit maps, risk prediction and the quest for effective interventions

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Addiction: from Latin addīctus; v: to be enslaved; n: a debt slave

The use and abuse of psychoactive substances by humans is at least as old as our ability to document our own existence, recurring as it does in some of the earliest known human texts (Crocq, 2007). Public perceptions of addiction have swung from being viewed as a moral failing or character flaw to the current view of addiction as a chronic psychiatric and brain condition. Modern neurobiological work is making tremendous strides in identifying the consequences of drug use and in detailing the neural circuitry underlying addiction, but there is much yet to be learned. What is the role of the environment? How are individual differences manifested? What is the influence of the developmental stage? What underlies successful treatment?

In this special issue of the European Journal of Neuroscience (EJN), we have compiled a series of empirical papers, targeted reviews and opinion pieces that provide a holistic overview of our latest understanding of addiction. The level of analysis for these questions extends from genes, molecules, circuits to behaviour and environment. Topics covered include addiction to alcohol and other drugs of abuse, prescription drugs, smoking, gambling and eating. In this editorial, we summarize this work, highlighting some common themes and threads and what we consider to be the most interesting results and future directions as well as open questions in the field. We start by discussing the experimental work (human vs. preclinical) followed by a summary of the reviews, which were mostly conducted using a translational approach (e.g. using evidence based on both clinical and preclinical studies). Specifically, we start by reviewing the human studies that highlight different approaches to

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exploring the risk of developing drug addiction, moving on to studies conducted in those who have already developed drug addiction and then to comparisons between drug with non-drug behavioural phenotypes of addiction and to intervention development. We highlight some clear gaps in the human literature and ways that were used to circumvent these gaps, concluding with future directions in the field. In the preclinical area, focus is on studying the brain in all of its complexity, exploring the impact of drugs of abuse on multiple neurotransmitter systems, regions and circuits. Importantly, behavioural biomarkers, and predisposition and comorbidity, constructs commonly explored in the human literature, have received attention here too. Predictably, these studies converge on developing timely intervention options, with commonalities across species noted (e.g., using replacement therapies in stimulant addiction). Interestingly, the reviews in this issue follow suit, describing different approaches to risk prediction, discussing the impact of drugs of abuse on multiple neural and behavioural systems, highlighting potential interventions and concluding with new horizons that take into account immunological, inflammatory and peripheral influences.

## Human studies

Neuroimaging was used to study the neural correlates of the core cognitive and emotional impairments in drug addiction, similar to the ones emphasized in the iRISA (impaired response inhibition and salience attribution) model (Goldstein & Volkow, 2002, 2011). For example, in populations at risk (binge drinking university students), evidence was presented for the need for more effort expenditure during response inhibition, as associated with disrupted functional connectivity between regions underlying adaptive attentional control; the suggestion that emotional (more arousing) contexts may mitigate this effect has clear therapeutic implications (Herman *et al.*, 2018). Drug-cue reactivity was studied in another sample of young problem drinkers where the finding of a differential sex (and severity) effect for processing alcohol cues in the striatum (less cue reactivity in females and those with lower alcohol use severity) has implications for both treatment and study design. That is, task paradigms using alcohol-related pictures may not be optimal to induce cue-reactivity in female drinkers, whereby the inclusion of different types of cues, such as stressors, may be needed (Kaag *et al.*, 2018). The latter results accord well with those of prior studies in drug-addicted individuals (Potenza *et al.*, 2012) although the former do not (Hester & Garavan, 2009), perhaps due to the inclusion of participants at different stages in the addiction process or because of inherent difficulties with human neuroimaging studies, which often rely on modest sample sizes and may not always have the power to correct for multiple comparisons or to conduct whole-brain analyses. Importantly, to circumvent these difficulties, large consortium data sets are now available including the IMAGEN sample, a longitudinal study of adolescence (Ewald *et al.*, 2016; Spechler *et al.*, 2018) and the ENIGMA sample, a cross-sectional multisite aggregation of adult addiction data (Mackey *et al.*, 2019), efforts that allow for highly powered studies of potential neural phenotypes in addiction. In the current issue, machine-learning techniques were applied to data provided by 1581 cannabis-naïve 14-year-olds (some who used cannabis at age 16, $N = 365$) to derive a sex-specific risk profile comprised of both psychosocial and brain prognostic markers likely to have preceded and influenced cannabis initiation in adolescence (Spechler *et al.*,

2018). In addition to studies in young populations at risk, the field has also employed a targeted gene approach whereby potential risk alleles are identified to contribute to differential structural and functional brain imaging patterns in drug addiction. For example, replicating and extending a previous study (Alia-Klein *et al.*, 2011), an interaction between a select gene (the monoamine oxidase A) and cigarette smoking was observed for both the morphological integrity of the orbitofrontal cortex and its functional connectivity strength. Specifically, individuals with the risk allele had greater orbitofrontal cortical grey matter volumes amongst non-smokers but not smokers, and this region's functional connectivity strength was higher for non-smokers than smokers (with a similar pattern for the hippocampus, and an opposite pattern for the dorsolateral prefrontal cortex and inferior parietal lobule that also correlated with smoking initiation and smoking years in smokers with the risk allele) (Shen *et al.*, 2018). Findings like these suggest that specific polymorphisms may contribute to susceptibility to drug dependence (here nicotine), invoking interactions with drug (i.e. environmental) influences on select brain regions and circuits.

Of note is that studies in at-risk individuals need to be assessed differently than studies conducted in individuals who meet criteria for the actual substance use disorder. In addition to the differences inherent in studying individuals with a clinical diagnosis, results from the at-risk samples may not generalize (and indeed be opposite) to the actual clinical disorder state. Thus, this point is important from both a practical (the difficulties, complexities and variability associated with studying individuals with a disorder) and a theoretical perspective (identifying the factors that predict transition to a disorder vs. those that characterize its different stages). Therefore, beyond studies in at-risk populations, studies in drug-addicted individuals are of crucial importance for understanding addiction. For example, such studies have established a generalized, although statistically modest, cognitive deficit in cocaine and alcohol addiction (Goldstein *et al.*, 2004) providing support for the need to enhance cognitive function to improve treatment outcomes (Aharonovich *et al.*, 2003, 2006). In this issue, a meta-analysis, whereby expected effects were explored across studies, has indeed provided support for a statistically subtle yet aberrant cognitive function (post-error slowing) in individuals with substance use disorder (Sullivan *et al.*, 2018). In this context, null and interesting results whereby treatment-seeking drug users have intact goal-directed control over action selection (Hogarth *et al.*, 2018) provide boundaries for the deficits previously reported, potentially pointing to the importance of the impact of abstinence length on cognition (Woicik *et al.*, 2009; Moeller *et al.*, 2010; Parvaz *et al.*, 2012; Bell *et al.*, 2014; Morie *et al.*, 2014); given some well identified limitations, these latest results will merit replication.

In addition to identifying biomarkers of vulnerability and common disruptions, or indeed intact functions in drug-addicted individuals, imaging studies can also contribute to treatment development and individual tailoring of treatment. For example, in a randomized, double-blind, placebo-controlled study, a mu opioid receptor antagonist (naltrexone) was shown to differentially amplify neural responses within two distinct regions of the salience network (the orbitofrontal cortex and the anterior insula) during successful motor impulse control (measured with a Go/No-Go task) in abstinent alcohol-dependent and polysubstance-dependent individuals, as predicted by trait impulsivity in the latter group (Nestor *et al.*,

2018). These results suggest that naltrexone may be beneficial for improving inhibitory control through differential mechanisms in different drug addiction subgroups, supporting the ultimate development of tailored interventions (e.g. engaging different brain regions in these different subgroups). In another double-blind, placebo-controlled, cross-over design, high-frequency repetitive transcranial magnetic stimulation (rTMS) to the posterior cingulate cortex and cuneus showed normalization of the processing of self-relevant stimuli (assessed using event-related potential P3 amplitudes and P3, N2 and P2 latencies) in cannabis users as compared with non-users (Prashad *et al.*, 2018). Thus, in addition to pharmacological approaches in combination with magnetic resonance imaging to measure outcomes, brain stimulation and EEG recordings expand the toolbox available to clinicians in treating addiction. This is especially welcome, given the substantially lower cost and enhanced portability of EEG vs. MRI, enhancing feasibility of large-scale roll-out in standard clinical settings.

An important question in the field is whether, and how, the neural substrates that underlie drug addiction can also be applied to non-drug-related behavioural addictions, such as gambling, sex addiction and binge eating disorder. For example, Angioletti and colleagues compared arousal levels during gambling in patients with Parkinson's disease using skin conductance and heart rate outcome measures (Angioletti *et al.*, 2018). Compared with recovered and 'never' gamblers, current pathological gamblers showed deficits on a standard decision-making task, while also exhibiting lower arousal during poor decisions. These results are consistent with one of the prominent theories in the field – the so-called somatic marker hypothesis, which arose from observations in neurological patients with ventromedial prefrontal cortical damage, who despite being relatively intact on standardized neuropsychological tests, showed both blunted affect/arousal and poorer decision-making on similar tasks (Bechara *et al.*, 1996; Damasio, 1996). The general notion is that appropriate somatic responses to poor decisions play a key auxiliary role in allowing for quick recalibration of strategy and that in the absence of appropriate communication/connectivity between the underlying neural systems, decision-making processes cannot recalibrate appropriately. It is quite intuitive to imagine how such disconnectivity might predispose to pathological gambling (Bechara, 2003), and this is also consistent with the literature in drug addiction (Verdejo-Garcia *et al.*, 2006; Verdejo-Garcia & Bechara, 2009).

Four reviews/theoretical accounts in these pages are also of note in this regard. (1) Spagnolo and colleagues provide a comprehensive review of the clinical neurobiological research on gambling disorder, with a specific emphasis on the neural circuits implicated in cueand stress-craving, taking substance use disorders as the major comparative example and describing studies that have evaluated rTMS as a therapeutic tool for targeting and restoring the neural alterations underlying the gambling urge in gambling disorder (Spagnolo *et al.*, 2018). (2) Myles and colleagues make a related call for the use of cognitive neuroscience to support public health approaches, such as the regulation of multiline slot machine design to minimize the harm of 'losses disguised as wins' (Myles *et al.*, 2018). That is, similarly to prior efforts in the drug addiction field (Martinez *et al.*, 2011; Balodis *et al.*, 2016), this call encourages the study of reinforcement learning towards the goal of reducing extended or repetitive use and gambling-related harm, representing a potential target to be leveraged clinically. (3) In the domain of eating disorders, Vainik and colleagues reviewed both cross-

sectional and longitudinal data of the relationship between food intake and body mass index, psychological variables (e.g. personality traits) and brain structure and function (encompassing the dopamine mesolimbic circuit, frontal cognitive networks and arousal/stress reactivity systems). They make call for unifying different eating-related constructs, such as food addiction, hedonic hunger, emotional eating and binge eating – into a single concept – uncontrolled eating (Vainik *et al.*, 2019). (4) Naish and colleagues provide a systematic literature review, finding partial evidence in support of a link between heightened response to experimentally induced stress and binge eating, calling for the identification of factors that modulate stress responses in individuals with this disorder (Naish *et al.*, 2018).

Open questions remain, of course. These include the difficulty in quantifying recent trends, which are dynamic and ever changing in the field of substance use and addiction. Here, using a newly developed online questionnaire assessing sociodemographic data and various relevant aspects of both legal and illegal substance use (such as consumption pattern and frequency), as well as risk-taking behaviour, a study provides detailed data about the substance use patterns, and associated major protective and risk factors, in more than 9000 college students from 17 different colleges in Berlin (Viohl *et al.*, 2019). A similar approach could be used to quantify these factors in other major cities and in other targeted high-risk populations. As mentioned above, the study of individual differences, including sex differences, is also of paramount importance. In general, there is marked underrepresentation of females in neuroimaging studies (or in clinical trials) of drug addiction (Zilverstand *et al.*, 2018). That said, the opposite trend also needs to be taken into account, since males are not well represented in the binge eating disorder literature (Naish *et al.*, 2018). New and exciting horizons to be explored include the contribution of peripheral measures, such as gut microbiota diversity, to brain function in substance abuse and drug addiction. Here, resting-state functional connectivity between the insula and several other brain regions was associated with bacterial microbiota diversity and structure as potentially modulated by tobacco smoking, providing a potentially novel therapeutic target for modulating brain connectivity (Curtis *et al.*, 2018).

## Preclinical models

As one might expect, model system studies in this special issue are mainly focused on the underlying mechanisms of drug addiction and related disorders. Animal experimental research on drug addiction can lay claim to a considerable degree of construct and face validity in modelling aspects of drug addiction in humans. In broad strokes, these studies focus on neurotransmission, brain regions/circuits, behavioural mechanisms and implications for treatment and they have the greatest potential when considered together; there is not one all-encompassing and ideal model of addiction but a richness of approaches, both theoretical and practical that mean significant advances have been made. The traditional focus on dopamine (DA) is exemplified by the importance of nucleus accumbens DA release as a neural substrate supporting adjustments in learned behaviour after a switch in expected stimulus-reward contingencies, contributing to our understanding of the role of DA in the persistent and maladaptive decision-making that characterizes drug addiction (Radke *et al.*, 2018). The role of DA is also explored in studies of heroin addiction where, similarly to cocaine addiction (Everitt, 2014), control over heroin-seeking behaviour appears

to shift to dorsolateral striatum DA-dependent mechanisms after extended training. Rats acquired heroin self-administration and were subsequently trained to seek heroin daily over prolonged periods of time under the control of drug-paired cues (Hodebourg *et al.*, 2018). Again, quantitatively similar to the patterns observed with cocaine, such dorsolateral striatum-dependent cue-controlled heroin seeking was disrupted by N-acetylcysteine, which restores cortico-striatal glutamate homeostasis (Hodebourg *et al.*, 2018).

Moving beyond DA, other studies also examined the function of glutamate and other neurotransmitters and receptors, identifying the following mechanisms: (1) a novel mGlu1 transmission mechanism for homeostatic plasticity in the nucleus accumbens medium spiny neurons (Loweth *et al.*, 2018) and glutamatergic plasticity in the effects of social defeat stress on a drug (MDMA) reward (Garcia-Pardo *et al.*, 2018); (2) reduced GABAAR transmission and diminished GABABR-mediated inhibitory signalling at entopeduncular nucleus-to-lateral habenula synapses during cocaine withdrawal (Tan *et al.*, 2018); and (3) a critical role of mu, but not delta or kappa, opioid receptors in context-induced reinstatement of oxycodone seeking and oxycodone self-administration (Bossert *et al.*, 2018).

Beyond the striatum, several studies in this issue focused on the role of the amygdala. Using electrical stimulation of rat brain slices and patch-clamp recordings, strong GABAergic inhibitory outputs to the major output zones of the amygdala were identified as inhibited by opioids and DA indicating that inhibitory projections from the main-island GABAergic neurons could influence multiple aspects of addiction and emotional processing (Gregoriou *et al.*, 2018). Using optogenetics in rats, a study by Tom and colleagues suggested a role for the central amygdala in excessive focusing of motivation and desire, generating addiction-like behaviours that persisted in the face of more rewarding alternatives and adverse consequences (Tom *et al.*, 2018). These studies can be read in the light of the physiological regulation of the amygdala. Converging evidence indicates that cholinergic signalling from basal forebrain projections to local nicotinic receptors is an important physiological regulator of the basolateral amygdala and that nicotine alters this region's role in cognition, memory, motivated behaviours (e.g. promoting responding for natural reward), emotional states (anxiety and fear) and taking and seeking drugs (Sharp, 2018). Beyond the amygdala, the functional interactions between the cerebellum and medial prefrontal cortex were highlighted in forming drug-cue associative memory, specifically the acquisition of cocaine-cue Pavlovian associations (Gil-Miravet *et al.*, 2018).

Of significant interest from a preclinical perspective, mechanistic approaches further used a behavioural biomarker (demand for cocaine) to predict progression to addiction and response to treatment with orexin-based therapies (James *et al.*, 2018). Efforts to avoid repeated drug injections and to allow assessment of initial subjective reward perception, in mice produced a condensed version of a place preference protocol, showing that a single exposure to both cocaine and amphetamine is sufficient to induce place preference (Runegaard *et al.*, 2018). These data also suggest that measuring VTA DA signalling prior to drug exposure can add to the tools available to further decipher the complex mechanisms underlying the progression from initial drug experience to escalating drug intake and addiction. Expanding the usual focus beyond impact on drug seeking or select cognitive and/or emotional function (e.g. reward perception), the effect of exposure to acute toluene

(the most widely misused inhalant) on sexual behaviour was studied in rats. Impairments in young sexually experienced rats were observed, and repeated toluene exposure during adolescence prevented the onset of copulatory behaviour, although this effect was transitory (Violante-Soria *et al.*, 2018). This type of study paves the way towards adding social neuroscience paradigms to basic neuroscience studies of addiction.

Another promising translational approach targets issues relevant to predisposition and comorbidity. For example, compared with sham-exposed rats, repeated blast traumatic brain injury (TBI)-exposed rats were more sensitive to oxycodone-associated cues during reinstatement, suggesting that repeated blast TBI may disrupt the relationship between oxycodone intake and seeking (Nawara-wong *et al.*, 2018). Inflammation in the frontal cortex may be one underlying mechanism, as suggested by a study using TBI to expose to cocaine self-administration (Vonder Haar *et al.*, 2018). These studies have clear clinical implications given the well-established increase in risk of substance abuse in those with a history of early life TBI (Cannella *et al.*, 2019).

Preclinical studies also explore novel treatment approaches. For example, insulin in the VTA reduced cocaine-evoked DA in the nucleus accumbens *in vivo* (Naef *et al.*, 2018) with other data highlighting the mechanistic underpinnings of R-modafinil and its bis(F) analogs as pharmacological tools to guide the discovery of novel medications to treat psychostimulant use disorders (Keighron *et al.*, 2018). However, one has to be cognizant of the evidence suggesting that DA agonists may precipitate *de novo* impulse control disorders, although this response can partially be attenuated by the beta-adrenoceptor antagonist propranolol (Cocker *et al.*, 2018). In general, chronic receptor engagement needs to be carefully considered. New insights relevant to treatment development are provided by an opinion that builds on pharmacological concepts related to homeostatic compensation subsequent to chronic receptor activation, calling for future large-scale studies directed towards identifying predictive biomarkers (of the development of impulse control symptoms during therapy with full and partial DA agonists across disease states) and potential new therapeutic targets (Napier & Persons, 2018). These efforts are consistent with similar studies in humans, such as those suggesting that methylphenidate, which binds to both the DA and norepinephrine transporters, could normalize brain (including connectivity) and cognitive function in cocaine addicted individuals (Goldstein *et al.*, 2010; Konova *et al.*, 2013; Moeller *et al.*, 2014). Modulation of cognitive deficits was also the substrate proposed to underlie the normalizing impact of nicotine administration on the dysregulated central oxytocinergic system in a mouse model of schizophrenia (Zanos *et al.*, 2018), which might partially account for the extraordinarily widespread use of nicotine in this disorder. Taken together, this focus calls attention to the self-medication hypothesis, where the drug is used to normalize function, calling for substitutive therapies in substance use and addiction.

Important to numerous preclinical and pharmacological studies is the issue of rate of drug delivery, whereby, for example, small differences in the rate of cocaine delivery influenced both the rate of rise of the drug and DA concentrations and psychomotor activity in rats (Minogianis *et al.*, 2018). In addition to providing support for prior studies that have suggested that a faster rate of rise of drug and DA concentrations might be an important factor in making rapidly delivered drugs (e.g. cocaine) more addictive (Volkow *et al.*, 2012),

this study has obvious relevance for the design of substitute medication-assisted therapies. Finally, gene editing vectors for studying nicotinic acetylcholine receptors in cholinergic transmission (Peng *et al.*, 2018) and layer-specific modulation of synaptic potentiation (of insular cortical changes in mice) (Toyoda, 2018) (Toyoda) offer new molecular, cellular and synaptic tools that could lead to novel discoveries of the mechanisms underlying addiction.

## Reviews

The experimental results described in the empirical work here can be better contextualized through the thorough translational reviews also contained in this issue. These reviews cast a wide net in summarizing a range of methodologies and key published reports where major findings from both animal and human studies are discussed. Similar to the research articles, understanding the risk towards developing drug addiction received focused attention. Beyond presenting the clinical and preclinical evidence supporting the deleterious effects of ethanol on the adolescent developing brain, this focus is clearly evident in the review on the mechanisms underlying the development of the prefrontal cortex as contributory to uncontrolled alcohol use in adolescence (Jadhav & Boutrel, 2018). These authors suggest that a late maturing prefrontal cortex (which contributes to advantageous decision-making and temporal processing of complex events) may represent a major candidate contributing to lifelong maladaptive responses, including increased vulnerability to developing substance use disorder later in life. In this context, we can mention a review that focuses on fibroblast growth factor 2 (FGF2), extensively studied for its role during development in cell proliferation, differentiation, growth, survival and angiogenesis, as well as for its role in adult neurogenesis and regenerative plasticity. In this review, accumulating evidence indicating the involvement of FGF2 in neuroadaptations caused by drugs of abuse (amphetamine, cocaine, nicotine and alcohol) is presented, suggesting that FGF2 is a positive regulator of alcohol and drug-related behaviours, which may provide a novel therapeutic approach for substance use disorders (Even-Chen & Barak, 2018). A genetic mechanism may be another (risk) candidate as suggested by a review that converged primarily on the role of nicotinic cholinergic receptor subunits, and other neurotransmitter systems as well as nicotine metabolism enzymes, to understand the various stages of nicotine addiction; interestingly, studies on the heritability of smoking initiation demonstrate substantial evidence for gene–environment interaction, although the precise molecular genetic mechanism(s) remains unknown (Sharp & Chen, 2018). Another thought provoking approach highlights the effect of paternal drug exposure to alcohol, cocaine, opioids and nicotine on behavioural and neurobiological phenotypes in the offspring in rodent models, with a special focus on addiction-relevant behaviours, but also cognition, anxiety and depressive-like behaviours (Goldberg & Gould, 2018). These authors invoke epigenetic changes that may be passed on through the germline, whereby this mechanism of epigenetic transgenerational inheritance may provide a link between paternal drug exposure and addiction susceptibility in the offspring. Review of the proteins and complexes contributing to epigenetic modifications (his-tone acetylation and deacetylation, histone methylation and DNA methylation) following drug experience, specifically in the nucleus accumbens, and the experimental manipulations of these proteins, provides an in depth glimpse into the potential for developing effective therapeutics to reverse or treat substance use disorders in

patients (Anderson *et al.*, 2018). Beyond cellular and molecular targets, potential interventions could also target change in core behaviours in drug addiction. For example, targeting reconsolidation and extinction to interfere with drug reward memories represents an important avenue for potential interventions, both pharmacologically (with the beta-adrenergic receptor antagonist propranolol and NMDA receptor glycine site agonists D-cycloserine and D-serine) and non-pharmacologically (with 'post-retrieval extinction' and 'UCS-retrieval extinction') (Liu *et al.*, 2018).

Several reviews focus on specific drugs and their effects on neurotransmission in targeted brain regions and circuits. For example, the role of midbrain DA in nicotine and alcohol reinforcement (Morel *et al.*, 2018) and the modulatory effects of cannabinoids on brain neurotransmission (Cohen *et al.*, 2019) shed light on the impact of both illicit and increasingly legal drugs on the brain. Other reviews call attention to specific brain (sub)regions. For example, evidence linking the nucleus accumbens shell to extinction and reinstatement of drug seeking sheds light on known heterogeneities in nucleus accumbens shell cell types, and their major afferents and efferents, suggesting that the functional specialization of the nucleus accumbens shell should be viewed in terms of the segregation and compartmentalization of its channels (Gibson *et al.*, 2018). Summarizing recent progress, it is suggested that cocaine-induced neuro-plasticity in the laterodorsal tegmental nucleus (a brainstem nucleus that sends cholinergic, glutamatergic and GABAergic projections to the VTA) cholinergic neurons contributes to the development and modulation of cocaine-related addictive behaviours (Kaneda, 2018). In the contribution from di Volo and colleagues, an interesting computational approach is taken to delineate potential circuit-level mechanisms responsible for alcohol-dependent dysregulation of DA release from the VTA into its projection areas (di Volo *et al.*, 2018). Invoking also GABA and glutamate, this model predicts that the impact of acute alcohol on DA release is critically shaped by the structure of the cortical inputs to the VTA.

Immunological and inflammatory influences are explored in three reviews. Linker and colleagues highlight the impact of drugs of abuse on glia-neural communication, and the profound effects that glial-derived factors have on neuronal excitability, structure and function, synthesizing the extensive evidence that glia have a unique, pivotal and underappreciated role in the development and maintenance of addiction (Linker *et al.*, 2018). Indeed, immunological changes are seen in clinical populations with substance use disorders, as well as in translational animal models of addiction. Hofford and colleagues highlight mechanistic findings showing causal roles for central and peripheral immune mediators in substance use disorder and appropriate animal models (Hofford *et al.*, 2018). Another avenue for enhancing specificity derives from accumulating knowledge of the effects of oxidative stress in the nervous system, evolving from strictly neurotoxic to including a more nuanced role in redox-sensitive signalling. Evidence for redox-mediating drugs as therapeutic tools (focusing on N-acetylcysteine as a treatment for cocaine addiction) is presented as one example (Womersley *et al.*, 2018).

## Conclusions

This special issue of EJN on ‘Addiction’ serves as a timely marker of the extraordinary advances that the field of neuroscience is making in the ongoing struggle against this condition, highlighting many of the novel approaches that are being leveraged in the effort to understand and combat this endemic societal problem. Nevertheless, it also serves as a call to arms to the community for renewed efforts and new insights. As we began above, for as long as human history has been documented, and likely long before that again, individuals amongst us – brothers, sisters, our children and loved ones – have suffered the consequences of addiction, and families continue to be ripped apart and devastated by this scourge. New challenges in this domain are emerging that will require novel approaches and large-scale political and societal commitment if we are to meet them effectively. The opioid crisis continues to produce infants that have been critically exposed *in utero*, born into this world with a neonatal abstinence syndrome (Larson *et al.*, 2019). It is abundantly clear that *in utero* exposure has long-term implications for brain development (Sargeant *et al.*, 2008; Ross *et al.*, 2015). Much of the opioid use in pregnant women arises from legally obtained prescription drugs rather than illicit sources, with a 2015 paper estimating that an extraordinary one-third of pregnant women were taking opioids (Anand & Campbell-Yeo, 2015). What should the standard of care be for these women? Is maintenance of the pregnant mother on opioids advisable or is detoxification a better approach (Caritis & Panigrahy, 2019)? Will these infants show greater vulnerability to addiction themselves as they grow into teenagers and meet the challenges of the young adult world? And what about the father’s role? Being raised without one or in an abusive, volatile, explosive and violent environment, or indeed through other types of paternal transgenerational inheritance, may all be crucial factors of need for greater scientific inquiry. To throw a wider net still, the role of many others in the community (e.g. those who predispose vs. protect against substance use) needs to be carefully explored within the social neuroscientific framework. In this vein, we can mention the widespread legalization of marijuana that is also proceeding apace, and while the policy and politics of this issue are not a focus here, the neuroscience community will have to concern itself actively with the implications for brain development and potential psychiatric sequelae, especially given the high potency synthetic cannabinoids that are now available (Harley *et al.*, 2010; Vaucher *et al.*, 2018; Cohen *et al.*, 2019).

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