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Mimicking human drug consumption patterns in rat engages corticostriatal circuitry

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A major focus of addiction research is the development of preclinical models that recapitulate key aspects of substance use disorder. Growing evidence indicates that the intermittent access (IntA) schedule of intravenous drug self-administration, which mimics the temporal kinetics of human drug use by separating brief periods of cocaine availability with longer periods of drug non-availability, promotes stronger and more persistent addiction-relevant endophenotypes compared to conventional continuous access procedures (Zimmer *et al.*, 2012; Kawa *et al.*, 2016; Algallal *et al.*, 2019; Allain & Samaha, 2019; James *et al.*, 2019b; Nicolas *et al.*, 2019; O'Neal *et al.*, 2019; Fragale *et al.*, 2020). In addition, the speed of drug delivery appears to play a critical role in determining behavioral outcomes, such that rapid drug infusions promote more robust addiction-like behaviors than sustained, continuous infusions (Allain *et al.*, 2017; Gueye *et al.*, 2019). Together, these data reflect an increasing recognition within the field that the *pattern* of drug consumption can be more important than the *amount* of drug consumed when modeling the transition from controlled to compulsive drug use in laboratory animals (Allain *et al.*, 2015).

Reflecting the relative nascence of the IntA procedure, only a few studies to date have leveraged this model to interrogate the brain systems involved in aberrant drug seeking. The majority of these studies have focused on nucleus accumbens (NAc). For example, several studies have reported that following IntA to cocaine, rats exhibit enhanced dopamine release and uptake in NAc; enhanced dopamine release in NAc is directly associated with cocaine motivation (Calipari *et al.*, 2013; Calipari *et al.*, 2015; Kawa *et al.*, 2019) and pharmacological blockade of dopamine signaling in NAc reduces cocaine seeking following IntA (Singer *et al.*, 2018). In another study where rats were identified as addiction-vulnerable or resistant following IntA heroin self-administration, chemogenetic inhibition of

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NAc direct medium spiny neurons (MSNs), or activation of indirect MSNs, suppressed cued reinstatement of heroin seeking selectively in vulnerable rats (O'Neal *et al.*, 2019; James & Mahler, 2020). In a series of recent studies, we have focused on the effects of IntA on the hypothalamic orexin (hypocretin) system, demonstrating that IntA to either cocaine or fentanyl is associated with increased numbers of hypothalamic neurons immunoreactive for orexin (James *et al.*, 2019b; Fragale *et al.*, 2020). We also reported that the IntA behavioral phenotype is attenuated by pharmacological blockade of orexin receptors (James *et al.*, 2019a; James *et al.*, 2019b; Fragale *et al.*, 2020; O'Connor *et al.*, 2020). Together these studies indicate that IntA promotes plasticity in several key addiction regions, including NAc and hypothalamus. To date however, the effect of IntA on prefrontal cortex (PFC), a key regulator of both hypothalamus and NAc in addiction (Marchant *et al.*, 2009; Stefanik *et al.*, 2013; Moorman *et al.*, 2015; McGlinchey *et al.*, 2016; James *et al.*, 2018), remains unclear.

In this issue of *Neuroscience*, Minogianis & Samaha (2020) examine how the combination of rapid and intermittent infusions of cocaine affects excitability of PFC and striatal regions. One group of rats had IntA to rapid infusions of cocaine (5 s infusion; IntA-5s), while another group had long access (6h; LgA) to slower infusions (90s; LgA-90s). Across 7 IntA/LgA sessions, total cocaine intake in the LgA-90s rats was approximately double that of the IntA-5s rats, however, in a subsequent test where cocaine motivation was assessed on a progressive ratio (PR) schedule of reinforcement, IntA-5s rats exhibited significantly greater responding. Following two additional IntA/LgA sessions, rats underwent a final 1h self-administration session on a fixed ratio 2 schedule (FR2) before being sacrificed, their brains being extracted and processed for *c-fos* mRNA. To avoid the potential confound of differential drug intake during this final session, infusions were delivered over 10s and capped at a maximum of 10 infusions for both groups. Compared to LgA-90s rats, IntA-5s rats exhibited greater *c-fos* mRNA in several PFC subregions, including ventrolateral and lateral orbitofrontal cortices (OFC) and prelimbic cortex (PL). IntA-5s rats also had higher *c-fos* mRNA in dorsal striatum; interestingly there were no differences in *c-fos* mRNA expression in NAc. Finally, correlational analyses revealed that in IntA-5s rats only, *c-fos* mRNA expression in ventrolateral and lateral OFC was positively correlated with levels in the ventrolateral portion of dorsal striatum; a similar relationship was observed between PL and the dorsomedial portion of dorsal striatum.

Minogianis & Samaha's paper offers an elegant and important step forward in identifying circuits recruited by a novel pattern of drug intake that promotes enhanced motivation for cocaine. Going forward, one key question will be to determine whether the corticostriatal circuits recruited during low-effort (FR2) cocaine self-administration are functionally linked to the stronger motivational phenotype in IntA rats observed on the PR test. Indeed, chemogenetic or optogenetic manipulation of these circuits will be useful for determining if they play a causal role in the expression of increased PR responding and other IntA endophenotypes, including increased economic demand, higher compulsive (punished) responding for cocaine and greater 'relapse' liability (Kawa *et al.*, 2016; James *et al.*, 2019b). An additional question relates to the relative contribution of the intermittency vs. the speed of cocaine infusions to the behavioral and neural outcomes observed here. Finally, it will be important to determine whether these findings extend to other drugs of abuse, especially given recent evidence that the IntA procedure is a powerful approach for

promoting a robust addiction-like state for opioids (O'Neal *et al.*, 2019; Fragale *et al.*, 2020; Martin *et al.*, 2020). Together with the current study, such studies will add to a burgeoning effort in addiction neuroscience – one that emphasizes the importance of preclinical models that utilize patterns of drug consumption that closely resemble those observed in humans.

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