A variety of preclinical literature demonstrates that aversive stimuli and drug stimuli can produce aversive or negative affect states marked by time-locked reductions in accumbal shell dopamine levels that can directly drive drug behaviors, which restore dopamine levels in-turn (Ungless *et al.*, 2004; Roitman *et al.*, 2008; Brischoux *et al.*, 2009; Wheeler *et al.*, 2011; Twining *et al.*, 2014). For example, Wheeler and colleagues found that a discrete palatable intraoral tastant became aversive (as indicated by oral rejection and aversive orofacial responses) and immediately reduced accumbal shell dopamine concentrations once the tastant was conditioned to predict impending injections of cocaine (20 mg/kg, ip within the next 45 min) or impending access to 2 hrs of cocaine self-administration (within the next 45 min) (Wheeler *et al.*, 2011). Notably, the dopamine reduction was time-locked to the behavioral aversion, which is consistent with the emergence of negative affective states (Koob & Le Moal, 1997 as cited in Wheeler *et al.,* 2011). Further, when a palatable intraoral tastant infusion was conditioned to predict *immediate* access to self-administration of *either* an i.v. cocaine injection or a concomitantly delivered intraoral tastant infusion, both the predictive tastant and the lever-pressing behavior resulted in *elevated* accumbal shell dopamine concentrations (Wheeler *et al.*, 2011). Finally, when a separate group of rats was trained to self-administer cocaine or intracranial stimulation, the administration of an intraoral tastant conditioned to predict impending access to cocaine self-administration (within the next 45 min) increased the frequency of intracranial self stimulation.

A variety of literature suggests that in addition to external cue associations, early drug-onset cues (experienced internally) can become associated with the later larger drug effects (Kim *et al.*, 1999). These interoceptive pharmacological cues may overshadow simultaneously present environmental cues and produce conditioned compensatory responses (states of negative affect that are driven by reductions in accumbal shell dopamine levels and oppose the subsequent drug responses). These conditioned compensatory responses are therefore thought to drive tolerance and can reinvigorate drug behaviors (since drug administration can restore the accumbal shell dopamine deficit and thus alleviate the negative affect). It is thought that subjects whose drug administration was not contingent, predictable, or self-controlled may experience stronger drive from interoceptive cues – as opposed to exteroceptive cues – since noncontingent drug experiences lack reliable external predictors by nature. This may result in greater interoceptive cue-driven compensatory conditioned responses that can contribute to greater levels of tolerance in individuals whose drug experience is uncontrollable and unpredictable. Since the ventral hippocampus is associated with relaying *interoceptive* information to the nucleus accumbens shell; whereas the dorsal hippocampus is associated with relaying *exteroceptive* information to the nucleus accumbens core (Barr *et al.*, 2018), the suggestion that greater interoceptive tone mediates tolerance and relapse suggests a possible role for the ventral hippocampus in mediating this process.

A variety of literature exists suggesting that noncontingent models of psychostimulant administration – in which the subject does not have control over drug administration – may result in greater drive from interoceptive cues (novel internal cues that are perfectly contingent with subsequent drug effects and therefore particularly salient). This may result from the fact that exteroceptive clues are limited or lacking in nonocontingent models. This may hold particular relevance to our studies, since the ventral hippocampus is associated with conveying interoceptive information to the nucleus accumbens shell whereas the dorsal hippocampus is more associated with processing exteroceptive cues (and connects to the accumbal core) (Barr *et al.*, 2018).

The interoceptive cues are thought to have greater influence of compensatory conditioned responses that can increase tolerance and produce negative affect states that drive drug behaviors in rats with history of self-administration (who have learned that drug exposure can restore the dopamine deficit associated with the negative affect states); whereas the conditioned compensatory responses can drive drug aversion in rats without a history of self-administration (who have not had the earned experience that drug taking can correct the conditioned compensatory response).

DRUG CUES, NEGATIVE AFFECT, CRAVING, AND RELAPSE

* Stress & negative affect increase cocoaine craving
  + Sinha 1999, 2000, 2003, 2006
* Increased craving positively correlates with depression and predicts relapse latency (Paliwal, Hyman, & Sinah 2008)

EXTEROCEPTIVE/INTEROCEPTICE: RODENTS

* “NAc MSN activity is driven by excitatory synapses emanated by inputs from limbic structures that encode different aspects of interoceptive and exteroceptive stimuli (O’Donnell et al., 1999)” as cited in Pignatelli et al., 2018
* Taste reactivity = affected by conditioned stimuli that engage sensory modalities independent of taste (Delamater et al., 1986;” as cited in Hurley et al., 2017
* Interoceptive conditioned stimuli (ICS)
  + Especially salient
  + Novel
  + Perfectly contingent w subsequent drug effect
  + Internal cue assoc w drug effect
  + May elicit condition compensatory respones (CCR) that mediate tolerance (Kim 1999) & relapse
    - Infra-admin assoc cues that = assoc w drug effect, contribute to opioid analgesia (Kim et al., 1999)
  + May overshadow simultaneous environmental cues (Kim et al. (1999)

A variety of literature suggests that in addition to external cue associations, early drug-onset cues (experienced internally) can become associated with the later larger drug effects (Kim *et al.*, 1999). These interoceptive pharmacological cues may overshadow simultaneously present environmental cues and produce conditioned compensatory responses (states of negative affect that are driven by reductions in accumbal shell dopamine levels and oppose the subsequent drug responses). These conditioned compensatory responses are therefore thought to drive tolerance and can reinvigorate drug behaviors (since drug administration can restore the accumbal shell dopamine deficit and thus alleviate the negative affect). It is thought that subjects whose drug administration was not contingent, predictable, or self-controlled may experience stronger drive from interoceptive cues – as opposed to exteroceptive cues – since noncontingent drug experiences lack reliable external predictors by nature. This may result in greater interoceptive cue-driven compensatory conditioned responses that can contribute to greater levels of tolerance in individuals whose drug experience is uncontrollable and unpredictable. Since the ventral hippocampus is associated with relaying *interoceptive* information to the nucleus accumbens shell; whereas the dorsal hippocampus is associated with relaying *exteroceptive* information to the nucleus accumbens core (Barr *et al.*, 2018), the suggestion that greater interoceptive \*\*\* mediates tolerance and relapse suggests a possible role for the ventral hippocampus in mediating this process.

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* Internal self-administration cues (SACs) = intra-administration cues (IAC)
  + May overshadow simultaneous exteroceptive stimuli.
  + Associations between an exteroceptive CS and a UCS suffer if the UCS is better predicted by the subject's own responses than by the external CS (Garrud, Goodall, & Mackin- tosh, 1981).

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