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Adult hippocampal neurogenesis as a target for cocaine addiction: a review of recent developments

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Abstract

Basic research in rodents has shown that adult hippocampal neurogenesis (AHN) plays a key role in neuropsychiatric disorders that compromise hippocampal functioning. The discovery that dependence-inducing drugs regulate AHN has led to escalating interest in the potential involvement of AHN in drug addiction over the last decade, with cocaine being one of the most frequently investigated drugs. This review argues that, unlike other drugs of abuse, preclinical evidence does not, overall, support that cocaine induces a marked or persistent impairment in AHN. Nevertheless, experimental reduction of AHN consistently exacerbates vulnerability to cocaine. Interestingly, preliminary evidence suggests that, on the contrary, increasing AHN might help both to prevent and treat addiction.

Introduction

Drug addiction is a chronic, relapsing disorder characterised by uncontrollable drug use, which is associated with maladaptive neurobiological and behavioural traits that may be intrinsic to the individual (i.e. vulnerability factors) or due to the neuroplastic effects of the drugs involved [1,2].

The hippocampus is a key part of the brain systems involved in cognition, emotion and reward and its functioning is disrupted in drug addiction [2-4]. A remarkable form of hippocampal plasticity is the generation of new neurons in the adult dentate gyrus (DG). Adult hippocampal neurogenesis (AHN) is present in many mammal and non-mammal species, but most research on the phenomenon has been carried out in rodents [5,6]. AHN was initially shown to be involved in the acquisition, consolidation and retrieval of hippocampal-dependent memories [3,7]. Later studies showed that AHN was also involved in the updating and forgetting of previously stored information [8,9] and in the regulation of emotional responses to challenging conditions such as chronic stress [3,10]. Although the existence and functional relevance of AHN in humans has been accepted for the past two decades, it has lately been called into question [11](*) and is currently hotly debated [12]. The latest evidence suggests that human AHN is abundant even in the senescence and is associated with healthy neurological and cognitive status [13-15]. The negative results and differences between studies may be due to methodological differences, for example in tissue processing protocols or the neurological illnesses of tissue donors [14](**). Setting this controversy aside, even in the event of humans displaying different AHN dynamics than rodents,

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AHN provides a valuable tool for basic research into hippocampal neuroplasticity in animal models of drug addiction.

Here we review current understanding of the role of AHN in cocaine addiction, focusing on the evidence relevant to the treatment and prevention of cocaine use disorders.

Cocaine does not always reduce AHN, but reduced AHN confers vulnerability to cocaine

Does cocaine reduce AHN?

The first link between AHN and drug addiction is that rodents that have been administered dependence-inducing drugs, including cocaine, show reduced AHN [16]. There are, however, many neurobiological mechanisms by which cocaine could modulate AHN, and both preclinical and clinical studies have shown that multiple potential regulators of AHN - neurotransmitters, neurotrophins, growth factors, hormones etc. - are disrupted during different phases of cocaine use and withdrawal in complex and time-dependent patterns that are consistent with both reductions and increases in AHN [17](*).

The acquisition and processing of cocaine-related memories is dependent on the hippocampus [4,18] and in rodents these processes are often assessed using the drug-induced conditioned place preference (CPP) paradigm. The preference for a maze compartment previously paired with a drug over a neutral maze compartment (CPP response) indicates that the drug is rewarding but also that hippocampal cognitive functions (contextual discrimination, learning and retrieval of memory for drug-stimuli associations) were engaged. Interestingly, rodents that have acquired cocaine-induced CPP do not show reduced AHN levels [19-21]. On the contrary, these rodents may even increase the maturation [21] and functional integration [19] of the population of immature adult-born neurons aged ~3 weeks or younger that show enhanced experience-dependent plasticity [3,6,22] (**Figure 1**).

The assumption of that cocaine *reduces* basal AHN has been supported by evidence that generation of new neurons (i.e. DG cell proliferation) is reduced shortly after (typically 24 h after) cocaine administration in rodents. It is not clear that this effect is dependent on the duration of the cocaine treatment and, importantly, it seems highly transitory (the relevant studies have been extensively reviewed elsewhere [17,21]). A long-lasting reduction in basal AHN after exposure to cocaine has been reported in a rat strain breed for a particular phenotype [23], but most studies report that basal levels of AHN return to normal a few days after cocaine administration ceases [17,21]. Thus although cocaine does modulate AHN, there is at present not evidence that there is an enduring reduction of basal AHN during cocaine withdrawal that contributes to maintenance of addiction-like symptoms. It is worth noting that, to the best of our knowledge, research on regulation of AHN by cocaine has been performed exclusively in male animals [4], revealing a strong sex bias that should be addressed in future studies. Another recommendation is that there should be basic research into AHN in novel animal models designed to capture the complex features of an addiction disorder and detect individual-level vulnerability factors [24]. In any case, examination of AHN in persons that abuse cocaine is still lacking and will undoubtedly provide a valuable evidence.

It should also be noted at this point that cocaine's effects on AHN may not resemble those of other addictive drugs. For example, ethanol induces a persistent reduction in AHN that lasts from adolescence to adulthood in rodents [25] and non-human primates

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[26], and there is evidence of reduced AHN in *post mortem* samples from people that abused alcohol [27]. On the other hand, methamphetamine withdrawal in rodents produces aberrant increases in AHN, which are associated with relapse [28]. The proposed roles of AHN in cocaine addiction (**Figure 2**) may not generalise to other drugs of abuse with different neurobiological effects.

Reduced AHN enhances motivation for cocaine and the persistence of cocaine-related memories

Regardless of whether cocaine reduces AHN, there are numerous genetic, pharmacological and environmental factors that can cause low ANH levels [6,17], inducing a potential neural vulnerability to the actions of drugs [16].

Self-administration is the gold standard technique for researching motivation for drugs in rodents. It involves assessing how frequently rodents press a lever that is - or was - paired with a drug infusion. The seminal study of the Eisch group [29] showed that rats with reduced AHN due to irradiation of the hippocampus self-administered more cocaine and worked harder for the drug than controls, indicating a greater desire for cocaine. A recent study in which AHN was abolished using a specific pharmaco-genetic strategy corroborated that loss of AHN was associated with higher motivation to self-administer cocaine and higher reinstatement of this behaviour (i.e. 'relapse') when re-exposed to a cocaine-associated cue [30](**) (**Figure 2**).

Research on cocaine-induced CPP also suggests that low AHN increases vulnerability to cocaine. Mice who were administered the anti-mitotic agent temozolomide systemically [21] and rats subjected to whole-brain irradiation [20] to reduce AHN acquired a cocaine CPP normally. Nevertheless, our study showed that the CPP was subsequently more difficult to extinguish; and more prone to reinstatement by administration of a low dose of cocaine (cocaine *priming*) [21] (**Figure 2**). Furthermore, expression of the CPP was mediated by alternative brain networks in the low-AHN mice [21]. Interestingly, this outcome converges with evidence on CPP based on a different drug, namely morphine [31] and with contextual fear conditioning [32], in which associated memories are acquired normally under low AHN but extinguish more slowly. While increased motivation for a drug or increased drug reward may influence CPP results; the fact that non-drug related memories - such as fear memories – may show a similar pattern [32] suggests that abnormal hippocampal memory processing is involved. Another feature of this phenomenon is that, as shown with morphine, the impairment in CPP extinction may be time-dependent, since it was observed for recent morphine CPP memories acquired under low AHN; but not after the memories became older (i.e. 'remote') and presumably stored in extra-hippocampal (cortical) regions [31].

In a separate group of experiments, AHN was reduced specifically during cocaine-withdrawal periods to investigate whether the adult-born neurons generated *after* cocaine exposure influenced subsequent addiction-like responses. Rats irradiated to reduce AHN after they had learned to self-administer cocaine made more level presses (the response used to administer the drug) when re-exposed to the self-administration apparatus after a period of withdrawal [29] or after *priming* with cocaine [33]. In the CPP paradigm, mice in which AHN was reduced during a period of withdrawal after cocaine conditioning retained their cocaine-induced CPP for longer and showed stronger *priming*-induced reinstatement than mice with normal AHN [21], probably because AHN contributes to forgetting of the CPP [34] (**Figure 3**).

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In conclusion, low AHN levels before or after cocaine exposure can exacerbate vulnerability to cocaine, both by increasing drug motivation or reward and by enhancing the persistence of cocaine-associated memories (**Figure 2**). In addition, reduced AHN in rodents has been associated with behavioural phenotypes linked to drug addiction, including impulsive traits such as preference for immediate rewards (DR Seib et al. personal communication in preprint), enhanced response to novelty [35], increased anxiety [36] and susceptibility to stress [3,37] (**Figure 2**). The basic scientific research suggests that reduced AHN is a vulnerability factor for cocaine addiction and that reduced AHN may be a neurobiological feature linking several mental illnesses – such as stress disorders or depression - to vulnerability to addiction in both animals and humans [16]. Once again, it is necessary to note that this conclusion is mostly based on research performed with male rodents [21,29,30,33], so potential sex differences in the observed effects or mechanisms are largely unexplored.

Potential benefits of increasing AHN to prevent or alleviate the behavioural effects of cocaine

Given that low AHN confers vulnerability to cocaine, it seems beneficial to normalize levels of AHN in risky conditions that are thought to involve a reduction in these neurons. However, the question arises about the desirability of increasing AHN beyond the 'normal' basal levels.

Unfortunately, the evidence that increasing AHN has a beneficial effect on cocaine-related responses is mostly indirect, being derived from non-drug-related studies or from 'non-specific' environmental or pharmacological interventions that enhance AHN but may also trigger wider neuroplasticity. This section focuses on the evidence that increased AHN can have a beneficial effect on the four main hippocampus-dependent processes involved in cocaine addiction.

Motivation for cocaine

Remarkably, environmental enrichment and/or voluntary running, which enhance AHN, have consistently reduced the propensity of rodents to self-administer cocaine and other drugs (the studies are extensively reviewed in [38-40]). This effect is found both in drug-naïve rodents that are first exposed to cocaine after experiencing the environmental intervention (i.e. the intervention is preventive) and when the environmental intervention is delivered during a drug withdrawal period, to rodents previously trained to self-administer cocaine (i.e. the intervention is used as a treatment) [38-40] (**Figure 2**). A pharmacological intervention involving intraperitoneal administration of cannabidiol, a pro-AHN compound, also resulted in lower rates of cocaine self-administration in mice [41]. Importantly, the protective effect of cannabidiol was inhibited by an anti-mitotic agent, proving that it was dependent on increased AHN [42].

Whilst these results are very promising, more studies are needed to confirm that the effectiveness of some of the interventions is dependent on increased AHN. It should also be tested whether increasing AHN by more specific experimental methods would be sufficient to reduce cocaine-seeking behaviour and cocaine intake.

Processing of cocaine-related memories

In contrast with the converging evidence that increased AHN reduces cocaine self-administration, when AHN-enhancing interventions are used as a 'preventive' approach *before* a cocaine CPP paradigm, reduced [41,43], unchanged [44,45] and even

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increased [46] cocaine CPP have been reported. The reason for these conflicting findings is unclear, although the use of (male) rodents of different strains and species may have contributed to the variability among studies [41,43-45]. Another possibility is that because increasing AHN may potentiate hippocampus-dependent contextual and associative memory [47], enhanced cognition may modulate the expression of the CPP response, independently of drug motivation and reward [17,31] (**Figure 2**).

Environmental interventions delivered *after* cocaine CPP acquisition seem to be more consistent in reducing the long-term maintenance of the cocaine-associated memory [17,44,46,48] - although one study specifically reported that AHN may not be necessary to the effectiveness of post-conditioning voluntary running [48] - (**Figure 2**). In addition to the environmental approaches, a reduced cocaine CPP maintenance was replicated in a study involving central administration of lysophosphatidic acid, a pro-AHN compound, which also showed an inverse correlation between AHN and long-term cocaine CPP expression [49]. These results are consistent with the notion that AHN plays a role in the forgetting of associative memories, as first revealed by the Josselyn-Frankland laboratory in 2014 [34] (**Figure 3**). This laboratory recently hinted that elevation of AHN would induce specific forgetting of recent memories acquired a short time previously and therefore still dependent on the hippocampus [8](**). This implies that increasing AHN may not be as effective in erasing distant memories of addiction, which are presumably stored in extra-hippocampal regions. Nonetheless, as with fear-based associative memory [50], it may still be possible to re-activate remote drug-associated memories (i.e. by re-exposure or recall) so they regain their hippocampal dependence and become once again susceptible to forgetting induced by AHN manipulations.

In conclusion, it is not clear that a permanent increase in AHN would result in vulnerability or protection to drug addiction based on effects on drug-associated memory processing, since AHN is involved in both acquisition and renewal of associative memories. Memories of a drug experience may be more easily acquired by individuals with increased AHN, but associations may also be more rapidly updated. On a different note, increasing AHN specifically during cocaine withdrawal would contribute to erasure of previous memories associated with cocaine, both as a result of extinction and forgetting (**Figure 2, 3**). Because extinction is an effortful process that requires the hippocampus [18] it may benefit from enhanced AHN [51] (**Figure 3**).

Cocaine-induced cognitive decline

Cocaine abuse is associated with a neurocognitive impairment that affects both prefrontal and hippocampal domains and predicts treatment drop-out and relapse into drug use [17,39], but there has been little fundamental scientific research into the role of AHN in cocaine-induced cognitive decline.

Experiments in our laboratory showed that mice in withdrawal from chronic cocaine had a persistent hippocampus-dependent cognitive impairment, although basal level of AHN (i.e. AHN measured in conditions of no stimulation – undisturbed animals -) was not altered [52](*). Nevertheless, the mice in the withdrawal group that had performed the cognitive assessment battery, showed reduced [52] or increased (MC Mañas-Padilla et al., unpublished results) levels of AHN compared with trained drug-naïve animals, and these effects seemed specific to the populations of new neurons whose neuroplastic properties allow their modulation by learning [52] (MC Mañas-Padilla et al., unpublished results). Therefore, although reduced baseline levels of AHN may not be a feature of mice in withdrawal from cocaine, they do not show normal AHN

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regulation when exposed to a cognitive challenge. Since there are certain requirements for a learning experience to stimulate AHN [53], this outcome is probably explained because cocaine-withdrawn mice did not reach a sufficient level of learning to stimulate AHN (in the case of reduced AHN) or their learning was excessively effortful (in the case of excessively increased AHN).

Strategies that increase AHN have been extensively linked to improved hippocampus-dependent memory (e.g. spatial memory, associative memory, memory for objects or places etc.) in 'normal', unimpaired rodents and in animal models of pathologies and insults [6,47]. Considering this, it is plausible that AHN-enhancing interventions would alleviate cocaine-induced hippocampal cognitive decline, although this has yet to be experimentally confirmed. It has also yet to be determined whether AHN plays an important role in typically prefrontal-dependent cognitive processes relevant to addiction such as impulsivity or decision making, although advances are being made in this regard (DR Seib et al. personal communication in preprint). Another interesting possibility is that increased AHN might provide a brain reserve that protects against the neurocognitive effects of cocaine and other drugs (**Figure 2**). There is already evidence that the spatial memory impairment induced by psychostimulants (methamphetamine) is smaller when they are administered to rodents housed in an enriched environment [54].

Emotional regulation

There is a bi-directional relationship between AHN and emotional regulation similar to that between AHN and learning: a negative emotional state may reduce AHN; and a reduced AHN may exacerbate dysfunctional emotional responses [3,10]. The brain circuit involved in the regulation of mood, stress and anxiety, of which the ventral hippocampus is a key component [3], overlaps with the brain circuit impaired by drug addiction [4,55]. Stress and negative affect are well-known factors in vulnerability to addiction and relapse into drug use [55,56] and mood and anxiety psychopathology are frequently comorbid with cocaine use [57]. A variety of environmental and pharmacological AHN-enhancing interventions have been shown to have anxiolytic and anti-depressive actions and increase resilience to chronic stress [3,10]. Research on a transgenic mouse model showing a specific increase in adult neurogenesis has confirmed the role of AHN in alleviation of anxiety and depression-like responses in stressful conditions [3,58,59](*). Although these studies were not related to drugs, it seems plausible that increased AHN would buffer the stressful and negative emotional states linked to cocaine vulnerability, withdrawal and relapse (**Figure 2**).

Conclusion

Overall the current basic scientific evidence in animal models supports the existence of a direct relationship between AHN and cocaine use and addiction. Reduced AHN has been consistently associated with cocaine vulnerability in rodents, and preliminary evidence suggests that increased AHN may in turn promote resilience to addiction. Interestingly, AHN seems to be involved in both the prevention and treatment of cocaine-induced effects. Given that the hippocampus is closely involved in regulation of memory, emotion and reward, AHN could simultaneously modulate processes in several domains, such as motivation for cocaine, cognition and emotion. We hope that this review will encourage further investigation of the role of AHN in addiction to cocaine and other drugs – especially by the use of methods that allow specific AHN manipulations - in both male and female individuals. Interestingly, hippocampal

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plasticity-enhancing strategies such as cognitive stimulation or physical exercise are already being used to treat substance use disorders [38-40].

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Figure legends

Figure 1. Immature hippocampal neurons are recruited for memory acquisition and subsequent processing. Figure shows a rat placed in a CPP maze compartment that has been paired with cocaine injections (resulting in cocaine-contextual stimuli associations). Hippocampal neurons generated in adulthood that are aged up to 3 weeks (blue), located in the DG granule cell layer (grey), are susceptible to enhance their survival, maturation and/or functional integration in the DG circuits in response to learning. This mechanism underlies many forms of hippocampus-dependent learning and seems involved in associative memories related to cocaine.

Figure 2. Summary of the main proposed roles for AHN in cocaine addiction. Importantly, these roles may influence both the prevention and maintenance of the addiction disorder. At present there is more empirical support for a link between reduced AHN and cocaine vulnerability; most of the evidence showing the benefits of increased AHN in animal models of addiction is indirect and should be confirmed with more sophisticated and specific AHN manipulations.

Figure 3. Potential role for AHN in forgetting and extinction of cocaine-related memories. Adult hippocampal neurons generated *after* memory acquisition (red) may interfere with neurons supporting previous memories (previous adult-generated neurons – blue - or old granule neurons – grey -) by competing for inputs. Newly-born adult hippocampal neurons could modulate synapses on the existing neurons [60], promoting forgetting of previous memory traces or hindering retrieval. Alternatively, this pool of new neurons may be recruited to support associative memory extinction, which is an effortful hippocampal process which involves a new learning that one stimulus no longer predicts the other. Therefore, increased AHN during cocaine withdrawal seems to reduce memories for previous cocaine experiences, whereas one would expect reduced AHN to enhance their persistence (**Figure 2**).

Annotations for the reference list

[8] (**) This manuscript does not deal with dependence-inducing drugs, but it provides solid evidence on the role of AHN in forgetting of associative memories. This effect is time-dependent and limited to recently acquired memories that are still stored in the hippocampus. These mechanisms should apply to cocaine-related contextual memories.

[11] (*) Álvarez-Buylla and collaborators challenged the existence of AHN in humans, which had been widely accepted up to this point on the basis of earlier findings. This manuscript attracted huge interest and prompted intense debate in the neuroscientific community and was followed by several high-impact studies from independent laboratories that provided evidence both for and against its findings.

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[14] (**) A key response to Álvarez-Buylla's group. Neurons with an immature phenotype were found to be abundant in the human hippocampus even in senescence. Methodologically this study sets the bar for future work, as confounding factors such as the fixative solution used or the (healthy) neurological status of the control individuals were controlled. Importantly, lower AHN was found in samples from patients suffering Alzheimer's disease, reinforcing the idea that reduced AHN is a disease mechanism.

[17](*). A recent review of the basic research on modulation of AHN by cocaine and on the many potential AHN-regulatory molecules that have been shown to be affected by cocaine exposure and withdrawal in both clinical and basic scientific studies.

[30](**) The authors provided strong evidence that reduced AHN is a vulnerability factor for cocaine addiction. An inducible transgenic mouse allowed a selective and controlled depletion of adult neurogenesis, which resulted in increased cocaine self-administration.

[52](*) In this basic scientific study we demonstrated deficits in hippocampus-dependent cognitive functions that persisted for at least 45-62 days of withdrawal from chronic cocaine. There were neurobiological alterations in the hippocampus of the mice, but basal levels of AHN were normal.

[58](*) A recent contribution from the Hen laboratory on the role of AHN in emotional regulation. Using sophisticated methods, this research group has consistently demonstrated a link between increased AHN and stress resilience.

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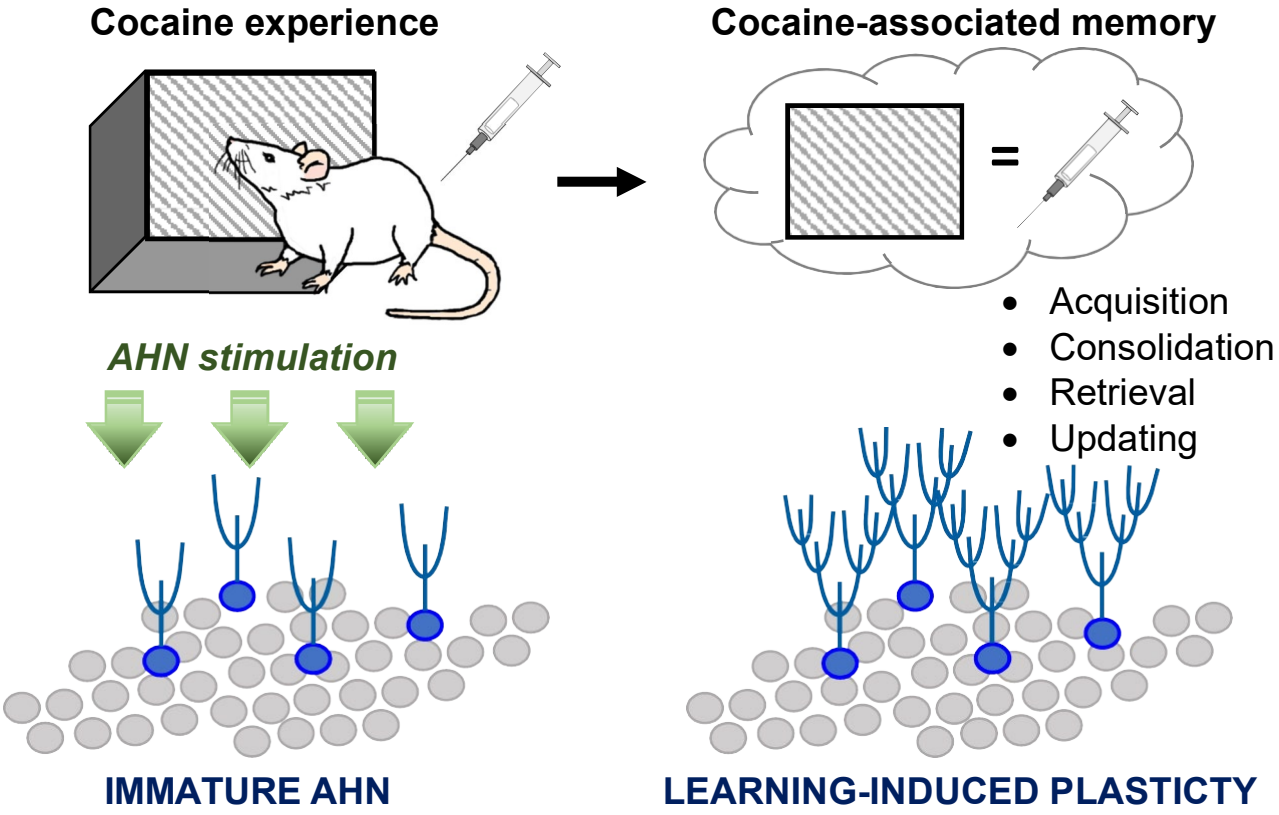

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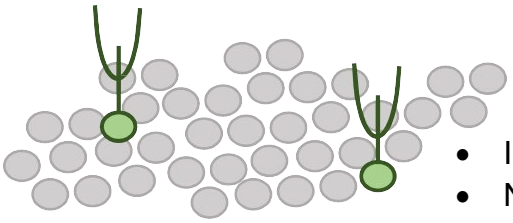
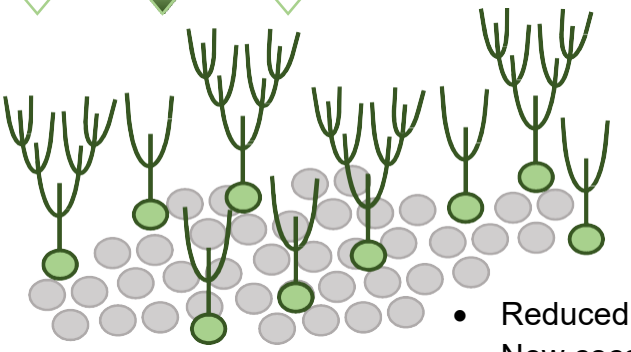


REDUCED AHN

- Increased motivation for cocaine
- New cocaine memories: non-flexible acquisition
- Previous cocaine memories: enhanced long-term maintenance
- Hippocampal-dependent cognitive impairment
- Vulnerable phenotypes (increased response to novelty or stress, impulsivity,…)

COCAINE ADDICTION VULNERABILITY

AHN-regulatory factors
(environmental, behavioral, pharmacological, genetic,…)



INCREASED AHN

- Reduced motivation for cocaine
- New cocaine memories: *potentiated acquisition?*
- Previous cocaine memories: potentiated extinction and forgetting
- Protection or alleviation from cognitive decline
- Stress resilience; other resilient phenotypes

COCAINE ADDICTION PROTECTION

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