toward the morphine-paired chamber. Future studies could address the relative impact of PVT→NAc inhibition on disruption of appetitive opioid memories versus disruption of aversive opioid withdrawal memories.

In summary, the novel findings presented by Keyes et al. (2020) provide an improved understanding of the neural circuits mediating opiate-associated memories, attributing distinct roles in opioid memory formation and retrieval to PVT projections to the CeA and NAc, respectively, thus enabling the fight against the opioid epidemic.

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Parental Bias Has Benefits

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In this issue, Laukoter et al., 2020 report that parent-of-origin-dependent expression is homogeneous across distinct cortical cell types and within individual populations. Conversely, they observe preferential sensitivity of astrocytes to altered doses of imprinted loci.

In eutherian mammals, a subset of maternal and paternal alleles are silent. Unlike transcriptional bursting, genomic imprinting results in stable parent-of-origin-dependent expression bias (Tucci et al., 2019). Genomic imprints are propagated across generations by epigenetic differences established in the respective parental germlines (Tucci et al., 2019). Imprints act in *cis*, such that adjacent, often clustered, genes are affected (Tucci et al., 2019). Overall, imprints affect the expression of ~150 mouse genes and many of the same human genes (Peters, 2014). The origin of genomic imprinting in placental mammals and its role in growth regulation suggest that genomic imprinting co-evolved with the divergent selective pressures on reproduction in eutherian mammal sexes. Hence, imprinting is typically modeled as either coadaptation to optimize fetal development and maternal provisioning or conflict, where males contribute a "selfish genome" to maximize maternal contribution (Peters, 2014). The maternal genome reciprocally moderates embryonic growth by silencing growth factors to provision for future pregnancies. But how does such conflict play out at a cellular level?

Parent-of-origin-dependent gene expression is widespread in the cortex (Perez et al., 2015; Tucci et al., 2019). Genomic imprints in the cortex regulate feeding, sleep, and behaviors that optimize maternal care. Dosage alteration of imprinted loci can cause developmental delay/disability, obsessive compulsive behaviors, gait ataxia, and sleep disturbance (Peters, 2014). Some imprinted genes regulating these behaviors exhibit consistent parent-of-origin effects across cell types during life, whereas others show spatial or temporal differences, including rare cases where the direction of parental bias changes during development (Babak et al., 2015; Laukoter et al., 2020). Whether the impact of imprinting is equivalent across or within cortical cell types is unknown and critical to mechanistic understanding of how imprints

regulate behavior. For example, previous FISH-based single-cell analysis of allelic expression in mouse embryonic fibroblasts with a mutant imprint control region for the *H19/Igf2* locus provocatively indicated heterogeneous rather than the anticipated uniform expression of the mutant parental allele (Ginart et al., 2016). To assess molecular and functional heterogeneity in the role of imprinting across cortical populations, Laukoter et al. compared imprinted expression and the consequences of uniparental disomies (UPDs; containing either two maternal or paternal copies) across cortical cell types. Their interrogation of specific disomies in individual cell types provides unprecedented resolution into the contribution of imprinting to cortical biology.

Laukoter et al. compared parent-of-origin-dependent expression across cortical cell types by using bulk and single-cell RNA sequencing (RNA-seq). Allelic expression was compared in cortices from reciprocal crosses of the divergent strains so that mono-allelic and parent-of-origin-dependent expression could be distinguished (Babak et al., 2008; Wang et al., 2008). Cortical populations were isolated with the following genetic reporters: Emx+ cortical and hippocampal projection neurons as well as olfactory bulb granule cells, along with Nkx2.1+ cortical and hippocampal interneurons. Bulk populations were initially used to compare whether imprinted genes exhibited consistent expression bias across cell types. Then, in a pioneering advance beyond evaluation of mono-allelic expression, imprinted expression was resolved and compared across populations of distinct single cells (Deng et al., 2014).

The role of imprinted clusters was compared elegantly across cortical cell types by inducing reciprocal UPDs. Mosaic analysis with double markers (MADM) was used to simultaneously induce UPDs and mark them with fluorophores reporting the parent-of-origin (Zong et al., 2005). In this scheme, recombination followed by co-segregation of two recombinant sister chromatids generates paired clones harboring either two maternal (mat) or paternal (pat) chromatids. The consequences of UPD of imprinted clusters was then evaluated. Particular attention was paid to chromosome (Chr.) 7 UPDs because it is syntenic to the regions responsible for Prader-Willi and Angelman syndromes. The molecular phenotypes of UPDs were then evaluated by bulk and single-cell RNA-seq, as well as clonal phenotyping.

Consistent parent-of-origin-dependent expression was observed across and within cortical cell types. The analyses evaluated twenty-five genes previously shown to exhibit imprinted expression in both the embryonic and adult cortex. These imprinted genes are distributed throughout the genome and are a mix of clustered and individual loci. In the future, single-cell resolution of the allelic dynamics of genes whose parent-of-origin-dependent expression changes during development would also be of interest (Babak et al., 2015). How stereotyped are the allelic dynamics in a population, and are there phenotypic consequences to deviations from the normal dynamics? In contrast to the consistent parent-of-origin-dependent allelic bias, 65% of the imprinted genes analyzed were differentially expressed in at least one pairwise comparison of cortical cell types. It would be informative to know whether the differential expression occurs during maturation of the same lineage or across cell types. The most pronounced differences appear to be across cell types where knowing the global differences would help to contextualize observations. Overall, this analysis clarifies that much of the impact of genomic imprinting on expression is consistent across the cortex.

The impact of UPDs on cortical cell types differs. UPDs of Chr. 7, 11, or 12 did not affect cell-fate specification. Curiously, the differential expression associated with UPD of either parent had more in common than differential expression associated with disomies from the same parent across cell types. Next, the authors focused on the impact of Chr. 7 UPD (UPD7) by evaluating its impact on neuronal, oligodendrocyte, and astrocyte lineages between embryonic day 15 and postnatal day 42. To ask how UPD7 impacted each population, the authors assessed enrichment of relevant gene ontogenies among the differentially expressed genes; these were "apoptosis," "growth/cell cycle," and "synapse." Unlike the neuronal and oligodendrocyte lineages, UPD cortical astrocytes consistently differed among these ontogenies across developmental stages. These data indicate that the consequences of UPDs are context specific.

Expansion of astrocytes harboring maternal disomies of Chr. 7 was deficient relative to patUPD astrocytes.This difference was not due to the imprinting of *Igf2*, located on Chr. 7. Fewer matUPD than patUPD cortical astrocytes were found at each stage from postnatal day 7 to postnatal day 90. Impressively, deletion of the pro-apoptotic gene *Bax* in matUPD7 astrocytes restored the population size to match patUPD astrocytes. Although no significant change in proliferation was seen at postnatal day 7 and postnatal day 21, it remains possible that a parental survival effect on astrocyte-specific progenitor proliferation over an earlier time period may be responsible for the different numbers of astrocytes seen. Also, it is worth considering whether the rescued matUPD astrocytes are functionally equivalent to patUPD astrocytes. Whether *Bax* deletion also rescues their differential expression between these populations would be informative. It will also be interesting to learn how imprinted tuning of the apoptotic threshold in astrocytes impacts cognition in future studies.

The relationships of UPDs to cell type, developmental stage, and phenotype are all exciting avenues of future research. The diminished matUPD astrocyte population is apparent by postnatal day 7, before a large increase in differential expression of UPD astrocytes at postnatal day 42. The origin of the cellular astrocytic phenotype at a developmental stage when differential expression is subtle relative to later stages raises the consideration that neurons and oligodendrocytes might also be affected functionally by these UPDs despite the absence of enrichment for consistent ontogenies at each developmental stage. Indeed, the maturation schedule of many neurons is earlier than astrocytes, begging the question of whether an altered dose of imprinted loci has common or cell-specific effects on cell types during equivalent maturation stages. In particular, it would be interesting to evaluate the consequences of UPD in populations, such as

hypothalamic neurons, where extensive imprinted expression has been observed and high selective pressure is inferred from the coadaptation model, given its role in the axis regulating fetal growth. Finally, the induction of UPD clones in wild-type backgrounds is an exquisite approach to isolate the role of imprinting on specific chromosomes. Continued application of this powerful new approach to link cellular and behavioral phenotypes will be of great interest.

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Piecing Together Cognitive Maps One Dimension at a Time

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In this issue of *Neuron*, Park et al. (2020) show that the brain forms unified cognitive maps of relational knowledge. The hippocampal-entorhinal region and medial prefrontal cortices spontaneously combine multiple, distinct rank orders to two-dimensional cognitive maps enabling flexible inference.

Imagine being the new coach of a soccer team. To get to know your players, you run different drills. First, you let players race each other to gauge their relative speeds. You observe that player A runs faster than player B and that player B outruns player C. Based on this, you can infer that player A is faster than player C, even if they have not directly raced. Such transitive inferences rely on relational networks in the hippocampus (Eichenbaum and Cohen, 2014). More broadly, the hippocampus is thought to form cognitive maps, the neural underpinnings of which have been uncovered in the context of navigation (O'Keefe and Nadel, 1978; Moser et al., 2017). Recent advances suggest the neural mechanisms that map space, for navigation, also encode abstract relations (Behrens et al., 2018; Bellmund et al., 2018), such as the relative running speeds.

To continue with our example, running speed is not the only relevant attribute of your players. In a second drill, they need to precisely aim their shots. These two abilities can be seen as the dimensions of an underlying space, where each player is positioned based on their relative speed and shot accuracy. You might use this to match players to positions in your line-up. Previous work suggests that the hippocampal-entorhinal region and medial prefrontal areas represent such relations in abstract spaces, akin to cognitive maps in navigation (Behrens et al., 2018; Bellmund et al., 2018).

However, it is unclear whether the brain combines individual attributes to such cognitive maps if they are learned separately, as would be the case with the two drills you run as the soccer coach. Further, you might run them with your defensive and your offensive players and thus learn about the skills of these groups independently. Park et al. set out to answer the question of whether the brain processes relations one dimension at a time or by combining characteristics into a unified cognitive map by integrating across distinct learning episodes.

To test this, participants were instructed that they were entrepreneurs learning about potential business partners to decide on future investments. These individuals, represented by face