(for example, a risk-averse participant succumbing to the influence of risk-seeking peers), activation in anterior insula and dorsal anterior cingulate cortex (dACC) increased. Although Chung *et al.*[1] interpret these responses as reflecting conflict between individual desires and group pressures, another recent study suggested that dACC integrates decision variables necessary for collective decisions[9]. These differing accounts of dACC function in social decision-making need not be mutually exclusive. For instance, recent work has demonstrated that the dACC can support different functions through distinct patterns of responses[10].

The study from Chung *et al.*[1] also raises questions that could inform models of social influence and conformity. For example, recent work has indicated that the mere presence of a peer boosts responses in neural networks implicated in attention, but not motivation[11]. These findings, when coupled with the results from Chung *et al.*[1], raise the question of whether attention and motivation affect social nudges through similar or distinct pathways. In addition, several studies have shown that functional connectivity between VMPFC and TPJ increases during social valuation[12] and social competition[13]. These observations raise the intriguing possibility that VMPFC responses to the other-conferred utility observed by Chung *et al.*[1] may partially depend on interactions with other regions such as TPJ. Characterizing how VMPFC functions as part of a larger network of interconnected regions could help advance models of individual differences, potentially clarifying the mechanisms that contribute to social nudges.

Chung *et al.*[1] provide a sophisticated account of how social information is integrated with individual preferences to guide behavior in the presence of a social nudge. Given the ubiquity of social influence, these findings have a wide range of implications. For example, understanding the mechanisms of social nudges could provide an opportunity to clarify the role of peer pressure in educational settings. In such settings, teachers could group students according to individual preferences so that social information can be used to maximize academic performance[14]. In addition, these new findings could also have implications for financial markets by curbing the deleterious effects of herd mentality[15]. These examples highlight the promise that may arise from a new mechanistic understanding of how we respond to social nudges.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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Lysosomes to combat Parkinson's disease

Ole Isacson

A study finds the transcription factor Lmx1b to be necessary in adults for preventing degeneration of midbrain dopamine neurons and implicates it in lysosomal function and regulation in these neurons.

The dopaminergic neurons of the midbrain (mDA neurons) are highly metabolic, have extensive synaptic connections and are under constant high oxidative stress[1,2]. When these neurons malfunction and eventually die, people will develop the movement disorder signs and symptoms of Parkinson's disease (PD). Although PD incidence increases markedly with population aging, the genes and factors that generate the mDA neurons are first expressed during development and then maintained at low levels in adulthood. Given that these neurons are postmitotic at birth, these functions must be optimized from early development in the fetal brain to adult and throughout aging. How is this accomplished, and what are the critical mechanisms that can enable mDA neurons to survive a lifetime? To understand what sustains mDA neurons, we need to start at the beginning, at their birth. Master transcription factors orchestrate the construction of the midbrain, and, by the first trimester, the cellular and physiological character of individual mDA neurons is fully determined. Could the establishment of these early transcription factors affect the chance that these neurons will survive adult pathological challenges and age? Laguna *et al.*[3] now show that when one of these developmental factors, LIM homeobox transcription factor 1β (Lmx1b), is ablated in mouse mDA neurons after the neuron is born, these neurons degenerate in adulthood. They also observed Lmx1b reductions in human PD.

The specific actors in these midbrain developmental cellular events are nuclear transcription factors such as Nurr1, Pitx3, Lmx1a, Lmx1b, Otx2, Foxa1 and Foxa2 (ref. 4). There have been hints that each of these factors can act both in development and adulthood to regulate functions critical to mDA neurons' survival[1,4,5]. Nurr1 controls levels of almost all DA transmitter–synthesizing enzymes, independently of cell type and mDA degeneration[4,6]. Developmental absence of Pitx3 results in a loss of the mDA neurons, whereas reductions of Otx2 and FoxA2 can result in a loss of function or susceptibility to degeneration of the mDA neurons[4,5,7]. However the relevance of these model studies to PD has been hard to interpret because the transcription factor losses have occurred *in utero* or during development, not in a cell- or region-restricted manner or during adulthood. To overcome some of these problems, Laguna *et al.*[3] used Cre recombinase under the control of the dopamine transporter (DAT) locus (*Slc6a3*), which is not active until after birth of all mDA neurons is complete, to ablate the transcription factors Lmx1a or Lmx1b in transgenic mice late in development. Expression of Lmx1a is known to be necessary for the production of specific mDA neurons

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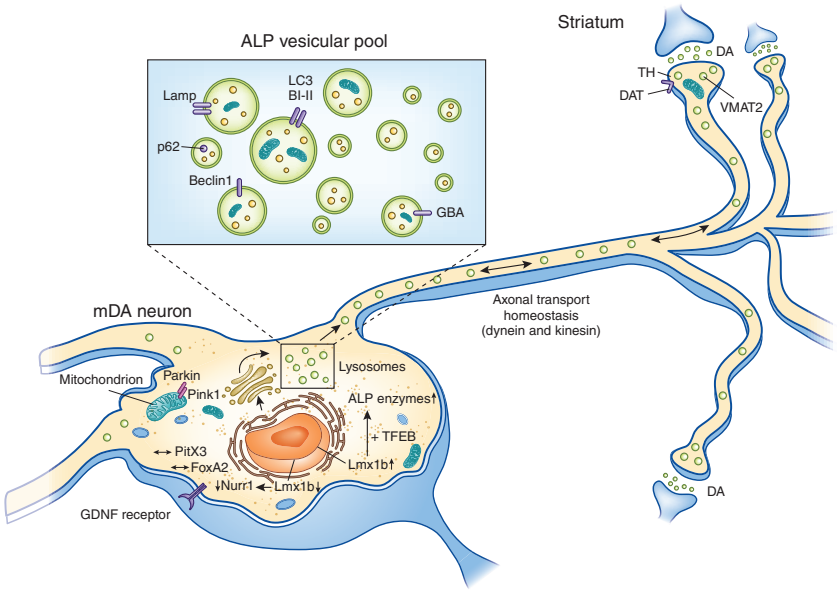

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Figure 1 The developmental transcription factor Lmx1b is involved in postmitotic mDA neuronal regulation of ALP proteins (Lamp1, Lamp2, beclin1, p62, LC3BI-II and cathepsin D) and influences expression of TFEB, which controls biogenesis of lysosomes in the ALP vesicular pool (inset). Reduced function of the lysosomal hydrolase GBA is a common risk factor for PD pathology, and mutations in mitophagy-related genes such as Pink1 and Parkin predispose individuals to early-onset PD. The absence of Lmx1b also reduces gene expression of proteins involved in axonal transport, including both dynein-dependent retrograde transport factors and kinesin-dependent anterograde transport factors. Finally, the loss of Lmx1b does not alter expressions of Pitx3 or FoxA2, but reduces the levels of the key mDA identity regulator Nurr1, which downregulates expression of dopamine transmitter–related proteins such as tyrosine hydroxylase (TH), DAT and vesicular monoamine transporter 2 (VMAT2), and presumably components of the GDNF trophic factor receptor.

during brain development, along with expression of the structurally related Lmx1b, which appeared at that stage to be involved primarily in general midbrain regional development. Unexpectedly, when the transcription factor Lmx1b was ablated in *DAT-Cre* mice, there were marked changes in autophagic lysosomal pathway (ALP) clearance systems[8] in mDA neurons, along with concurrent reductions in Nurr1 and axonal transport proteins[3] (**Fig. 1**). The authors found that such a Lmx1b loss led to dysfunction, as measured by reduced synaptic DA levels in targets of the mDA neurons, and eventually to degenerative loss of first striatal DA axons and then mDA neurons themselves. They also examined tissues from PD patients post-mortem. Their data, albeit limited to three subjects, suggest that Lmx1b is also downregulated in patients' mDA neurons.

The loss of ALP functions associated with diminished Lmx1b described by Laguna *et al.*[3] contributes to our understanding of what initially goes wrong in cells to cause PD. Several PD-associated genes with recessive (loss of function) Mendelian inheritance (for example, Pink1 and Parkin) have been proposed to promote the autophagic removal of damaged mitochondria, organelles that themselves are uniquely susceptible to damage in mDA neurons[8,9]. The pathophysiology of LRRK2, a key protein implicated in familial PD, may also involve ALP clearance capacity. More recently, it has been shown that another protein implicated in both familial and sporadic (non-familial) forms of PD, α-synuclein, depends in part on adequate physiological clearance by ALP enzymes and the action of the ubiquitin ligase Nedd4 (refs. 9,10).

Transcription factor EB (TFEB) is a critical overall regulator gene of lysosomal biogenesis, autophagy and degradation by lysosomes[11]. Overexpressing TFEB in the brain in neurodegenerative animal models increases the capacity for lysosomal protein clearance of α-synuclein, whose accumulation is known to be toxic to mDA neurons[9,10,12] and to create intracellular protein clumps named Lewy bodies[12]. Conversely, blocking TFEB results in reduced lysosomal capacity, α-synuclein oligomer accumulation, DA neuron pathology and cell death[11,12]. Laguna *et al.*[3] found that TFEB is downregulated by *Lmx1b* gene ablation in mDA neurons.

Heterozygous mutation of the lysosomal glucocerebrosidase GBA1, inducing a 30–50% loss of enzyme function, ranks as the most frequent genetic risk factor for PD and dementia with Lewy bodies[9]. Inhibition of GBA1 decreases pH-dependent autophagy and lysosomal degradation of α-synuclein[9]. Examination of brain tissue from patients with sporadic PD suggests that deficits in ALP are fundamental to PD. The numbers of lysosomal-associated membrane protein-1 (LAMP-1)-positive lysosomes are reduced and many autophagic vacuoles are present in the substantia nigra of PD patients[13]. The finding by Laguna *et al.*[3] of reduced Lmx1b in the substantia nigra in PD, along with the cellular data from their animal models showing diminished ALP function, is consistent with such interpretations.

Pathological and familial genetic studies thus both point to ALP systems as failing in PD. Most PD cases do not have a simple hereditary explanation, but the convergence of genetic, environmental and age-related factors over time appear to produce a phenocopy of the same cellular biochemical deficits[14,15]. GBA enzymatic activity is decreased in the brains of patients with sporadic PD, causing its substrate lipid, glucosylsphingosine, to accumulate[14]. In their sixties, even PD patients whose disease is not associated with mutations in *GBA* have marked reductions in GBA activity in several brain regions, as well as increased levels of glucosylsphingosine, in comparison with age-matched controls[14]. Notably, these GBA activity reductions are found in people without disease in their seventies[14], suggesting that the endolysosomal system is gradually impaired in normal aging, which could explain the rapid increase in PD and related neurodegenerative diseases seen with age[14]. These data suggest that the aging of lysosomal systems is more rapid in those at risk for PD[14]. Thus, the surprising new evidence that the transcription factor Lmx1b supports ALP systems and helps maintain the structure, axonal transport and survival of mDA neurons from birth into adulthood[3] further strengthens the rationale for developing ALP-related diagnostics and therapeutics to prevent and treat PD.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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