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The neuronal stimulation–transcription coupling map

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Neurons transcribe different genes in response to different extracellular stimuli, and these genes regulate neuronal plasticity. Thus, understanding how different stimuli regulate different stimulus-dependent gene modules would deepen our understanding of plasticity. To systematically dissect the coupling between stimulation and transcription, we propose creating a 'stimulation–transcription coupling map' that describes the transcription response to each possible extracellular stimulus. While we are currently far from having a complete map, recent genomic experiments have begun to facilitate its creation. Here, we describe the current state of the stimulation–transcription coupling map as well as the transcriptional regulation that enables this coupling.

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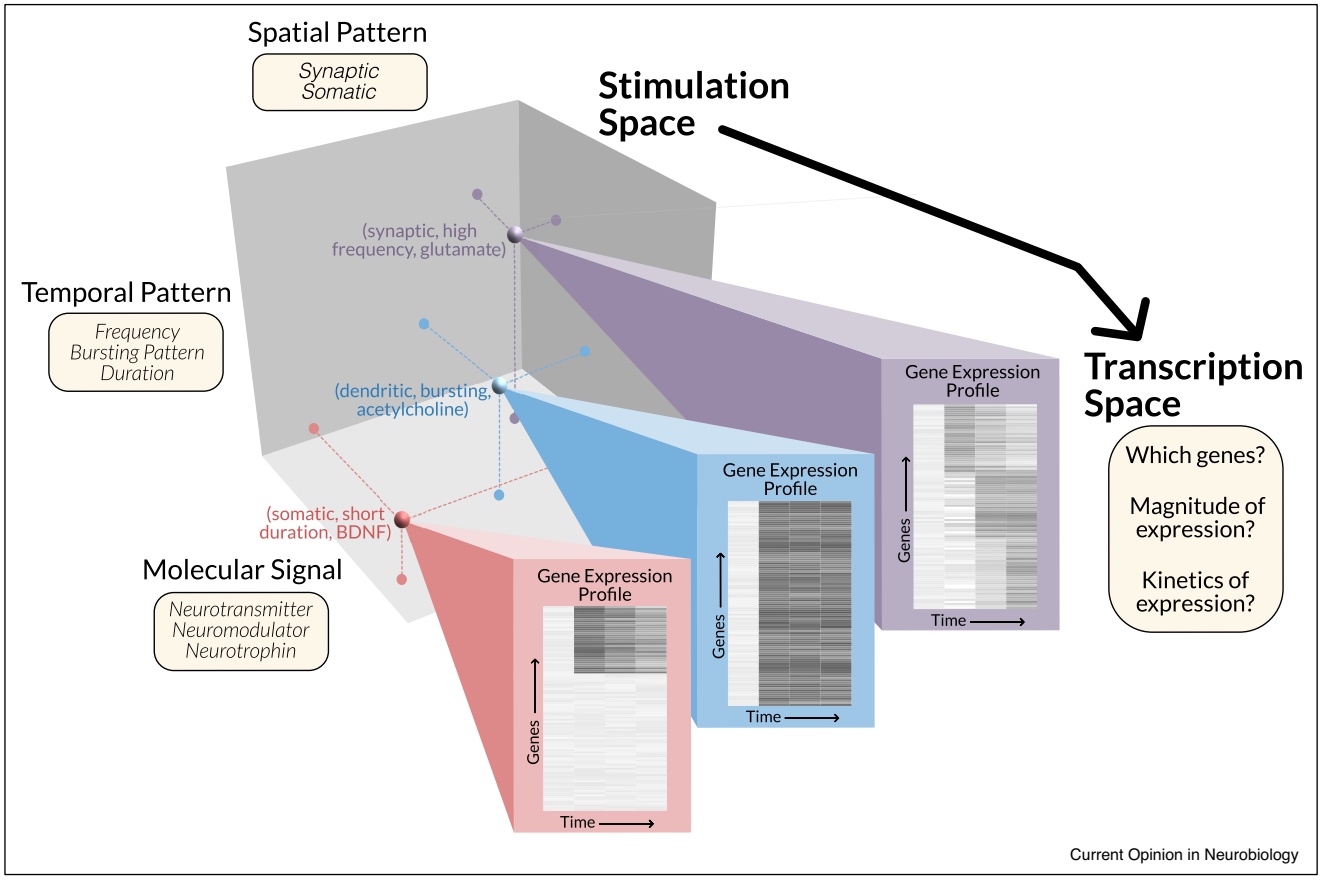
Introduction

Neurons transcribe different subsets of neuronal-activity-regulated genes (ARGs) in response to different extracellular stimuli [1,2,3••,4–9,10••,11–14,15••]. Thus, a vast number of different stimuli could each be coupled to a unique transcription program. We have known since the 1980s that the nature of neuronal stimulation, including its intensity and temporal pattern, determines the magnitude of induction of a few individual ARGs, such as *Fos* and *Egr1* [1,2,3••,4–7]. More recently, genomic studies of hundreds of ARGs have begun to expand such findings to reveal how different stimuli are coupled to the ARG program as a whole [8,9,10••,11–14,15••].

Understanding this coupling between stimulation and transcription could be a new and powerful route toward understanding how ARGs orchestrate neuronal-activity-dependent plasticity. ARG transcription contributes not only to neuron-wide plasticity like homeostatic synaptic scaling [16], but also to synapse-specific plasticity (e.g. long-term potentiation [17], which may occur via synaptic tagging [18]). Thus far, this ARG-dependent plasticity has primarily been investigated using single-gene knockouts and total blockades of transcription [16,17]. For example, knockout mice have revealed that *Arc* and *Homer1a* are important for homeostatically tuning synaptic strength [19,20], that *Npas4* and *Bdnf* regulate inhibition onto excitatory neurons [21–23], that *Nptx2* promotes excitation onto inhibitory neurons [24], and that *Igf1* cell-autonomously regulates inhibitory inputs onto vasoactive-intestinal-peptide-expressing interneurons [80]. However, hundreds of ARGs are induced in response to stimulation, making it laborious to use single-gene manipulation to link each gene to a specific type of plasticity. Because different stimuli induce different types of plasticity [25], one alternative to single-gene manipulation is to test the functions of ARG modules defined by the stimuli that induce them. This approach will require identifying stimulus-specific modules and manipulating module-specific regulatory mechanisms. Thus, to enable this approach and reveal new roles for ARG modules in plasticity, it will be important to understand how each type of stimulation is coupled to an ARG expression program as well as the transcriptional regulation that establishes such coupling.

To systematically assess stimulation–transcription coupling, we propose creating a stimulation–transcription coupling map (Figure 1). This map will describe how stimulation space (which encompasses all possible variation in stimulation) maps onto transcription space (which encompasses all possible ARG expression programs). Specifically, stimulation space includes the neurotransmitter or neurotrophin stimulating the neuron, the valence of this stimulus (excitatory or inhibitory), and its temporal or spatial pattern. Transcription space includes which genes are regulated by stimulation as well as the magnitude and kinetics of their expression. While we are far from a complete stimulation–transcription coupling map, genomic analysis has dramatically improved our ability to draw the coupling map by enabling assessment of all of transcription space in a single experiment [8,9,10••,11–14,15••]. These genomic experiments have begun to reveal principles of stimulation–transcription that enable prediction of which genes modules will be induced by which stimuli. Here, we will summarize these principles and the transcriptional regulation that establishes them.

Figure 1



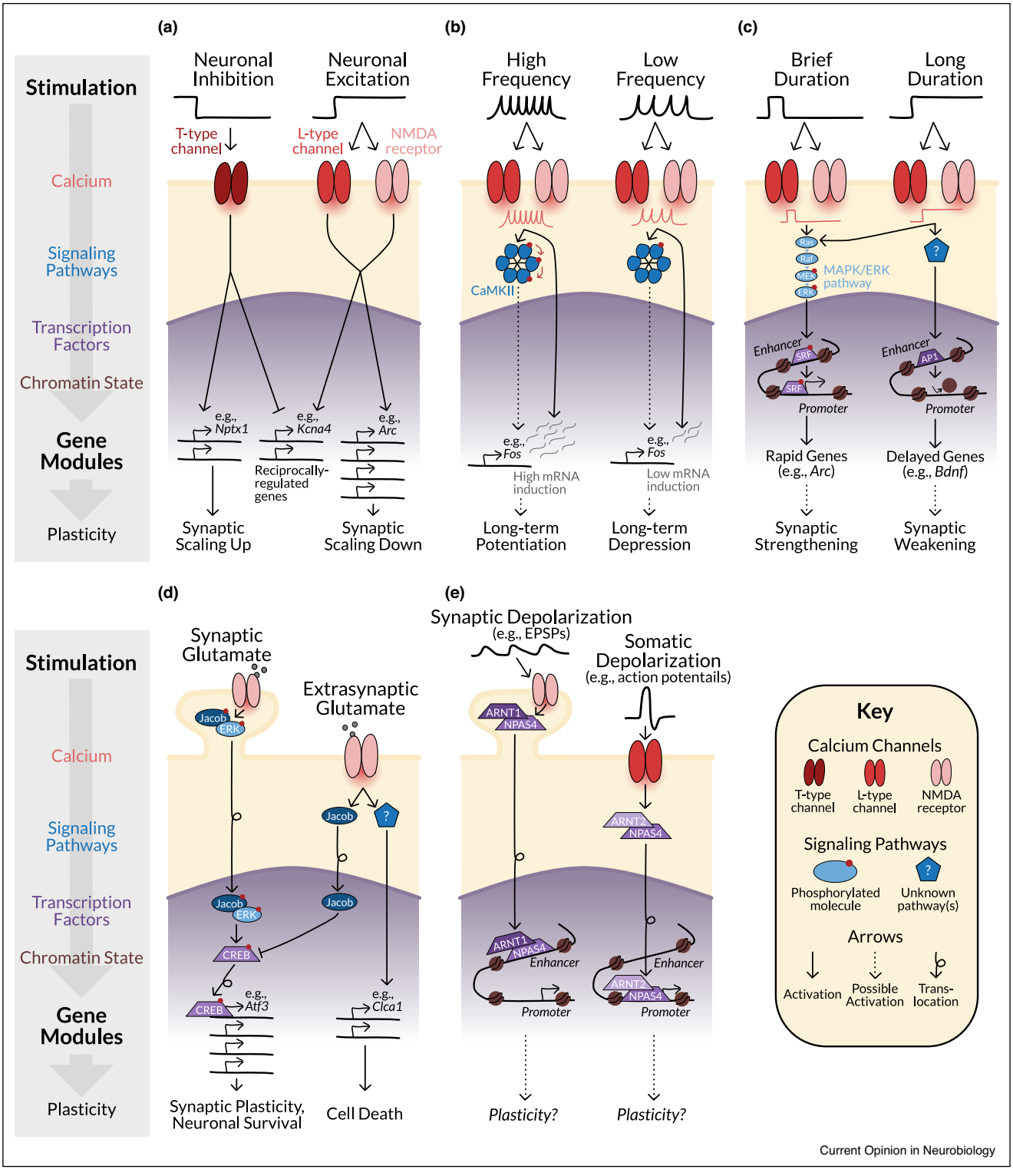
The neuronal stimulation–transcription coupling map.
We propose creating a stimulation–transcription coupling map that would link stimulation space (all possible different stimuli) to transcription space (all possible transcription programs). Here, we show an example of three theoretical couplings between stimulation space and transcription space, depicted on a simplified three-dimensional stimulation space defined by the spatial pattern (x) molecular identity (y), and temporal pattern (z) of the stimulus.

Principles of stimulation–transcription coupling

Early studies of a few individual genes revealed the first principle of the coupling map: increased neuronal activation results in increased transcription (Figure 2b). In cultured neurons, transcription of the ARG *Fos* increases with increasing frequency of electrical stimulation [3••], longer durations of membrane depolarization [7], and greater concentrations of nicotine [1]. The magnitude of *Fos* transcription also depends on the bursting pattern of electrical stimulation: it is greater in neurons stimulated with short bursts and short inter-burst intervals compared to long bursts with long inter-burst intervals, even when both patterns have an equal number of total spikes [3••,6]. In addition to an increase in the magnitude of transcriptional induction, the number of genes induced also increases with increasing durations of electrical stimulation [4]. Thus, pre-genomic studies revealed that the frequency, intensity, and duration of stimulation, as well as its temporal organization, determines which ARGs are transcribed and the magnitude of their transcription.

Genome-wide analysis has confirmed these principles and revealed new ones. First, neuronal excitation and inhibition regulate partially, but not entirely, reciprocal gene programs [15••,26,27] (Figure 2a). Inhibition might be expected to induce an entirely reciprocal program to excitation, where all genes upregulated (or downregulated) by excitation are downregulated (or upregulated) by inhibition. Instead, the inhibition and excitation gene programs appear to be only partially reciprocal: In cultured neurons, ~45% of the genes differentially regulated in response to inhibition via sodium channel blockade are reciprocally regulated in response to excitation via synaptic stimulation [15••,27]. These same reciprocally regulated genes make up only 7–32% of the excitation-regulated gene program (because excitation regulates more genes than inhibition) [15••,26,27]. This leaves a

Figure 2



Principles of stimulation–transcription and its transcriptional regulation.
(a) Neuronal excitation and inhibition regulate different, partly reciprocal gene programs, with excitation regulating more genes than inhibition. **(b)** Neurons stimulated at higher frequencies transcribe ARGs at higher levels. **(c)** Neurons stimulated for brief durations selectively transcribe a rapid gene module, whereas neurons stimulated for longer durations also transcribe a delayed gene module. **(d)** Stimulation of synaptic NMDA receptors induces transcription of synaptic plasticity and pro-survival genes, whereas stimulation of extrasynaptic NMDA receptors induces transcription of cell-death genes. **(e)** Different sources of depolarization engage different transcription factor complexes.

substantial fraction of genes that appear to be uniquely, rather than reciprocally, regulated by either inhibition or excitation. These uniquely regulated genes may be important for the plasticities that occur specifically in response to inhibition (e.g. homeostatic synaptic strengthening) or excitation (e.g. homeostatic synaptic weakening) [28]. For example, a gene upregulated by elevations in activity, *Homer1a*, is required for homeostatic synaptic weakening [20], whereas a gene upregulated by reductions in activity, *Nptx1*, is required for homeostatic synaptic strengthening [15••]. In contrast, reciprocal regulation of a single gene has yet to be functionally implicated in opposite homeostatic plasticities.

Genome-wide experiments have also revealed that neurons stimulated by excitatory neurotransmitters, neurotrophins, or neuromodulators transcribe overlapping gene programs. Excitatory neurotransmitters induce transcription primarily via membrane depolarization, whereas neuromodulators and neurotrophins mainly act through metabotropic or tyrosine kinase receptors [29]. Thus, these distinct classes of stimuli might be expected to regulate widely different gene programs. Instead, using separately published gene lists from cultured cortical neurons, we calculate that 43% (16/37) of genes induced in response to the neurotrophin BDNF [30] are also induced in response to membrane depolarization [10••]. Similarly, 27% (30/111) of genes induced in cultured cortical neurons by synaptic glutamate stimulation are also induced by stimulation with forskolin, a proxy for neuromodulator stimulation [31]. Thus, many different non-inhibitory stimuli likely regulate stimulus-specific gene modules drawn from a common set of ARGs.

In addition, different temporal patterns of stimulation are coupled to different transcription programs, specifically to different kinetically defined gene modules [9,10••]. In both cultured cortical neurons and the cortex *in vivo*, short durations of neuronal activity selectively induce a rapidly induced gene module ('rapid genes') that includes *Fos* and *Arc*, whereas longer durations of activity also induce a slowly induced gene module ('delayed genes') that includes *Bdnf* and *Nptx2* [10••] (Figure 2c). Similar kinetically defined modules may also be differentially regulated in cultured dorsal-root ganglion neurons in response to different bursting patterns. 71% of genes induced by electrical stimulation with long bursts and long inter-burst intervals are induced rapidly, whereas only 4.5% of genes induced by short bursts and short inter-burst intervals are induced rapidly [9], suggesting that long bursts may primarily induce 'rapid genes' and short bursts, 'delayed genes'. Kinetically defined rapid and delayed gene modules exist in many inducible systems: rapid primary response genes (PRGs) start to be transcribed within five minutes following stimulation, whereas delayed PRGs and secondary response genes are induced in tens of minutes to hours [32]. Therefore, the neuron makes use of the multi-wave kinetic structure of the ARG program to induce different genes in response to different temporal patterns of stimulation.

Finally, different spatial patterns of stimulation are coupled to different gene expression programs (Figure 2d). Pharmacological separation of synaptic and cell-body NMDA-receptor stimulation in cultured neurons revealed that stimulation of synaptic NMDA receptors induces transcription of far more genes than stimulation of cell-body receptors [14]. The genes uniquely induced by synaptic NMDA receptor stimulation are pro-survival genes, whereas those uniquely induced by somatic NMDA receptor stimulation are cell-death genes, revealing a potential mechanism for glutamate-driven excitotoxicity [14]. Furthermore, synaptic depolarization from excitatory post-synaptic potentials (EPSPs) and somatic depolarization from action potentials differentially regulate the binding partners and binding sites of the activity-regulated transcription factor, NPAS4 [33••] (Figure 2e). This differential binding suggests that EPSPs and action potentials may also regulate different ARG programs.

Mechanisms of stimulation–transcription coupling

The neuron implements stimulation–transcription coupling by transforming each stimulus into a transcriptional output through multiple layers of regulation, including calcium channels, cell-signaling pathways, transcription factors, and chromatin state (Figure 2). For example, brief stimulation is coupled to induction of rapid genes through the MAPK/ERK pathway, which is required for rapid gene induction [10••].

First, the stimulus determines the location of elevated calcium within the neuron [34–39,40•] and its temporal pattern of influx [40•,41,42], which can influence transcription [15••,43]. Activating stimuli, such as membrane depolarization or synaptic glutamate, drive gene induction via calcium influx through L-type calcium channels or NMDA receptors [29]. The temporal pattern of this calcium influx reflects the temporal pattern of spiking or glutamate stimulation [40•,41,42]. The spatial pattern of calcium influx is also dependent both on the temporal pattern of glutamate stimulation as well as on the spatial pattern of membrane depolarization [33••,40•]. For example, synaptic EPSPs drive gene induction through NMDA receptors, whereas somatic action potentials drive gene expression through L-type calcium channels [33••]. Unlike activating stimuli, neuronal silencing through sodium channel blockade appears to drive gene induction through T-type calcium channels rather than L-type calcium channels or NMDA receptors [15••]. Finally, stimulation of metabotropic receptors results in release of calcium from intracellular stores rather than an influx of extracellular calcium [37]. Compared to

extracellular calcium influx through channels, calcium from intracellular stores spreads further throughout the neuron [36,37]. The extent of calcium spread is important for gene induction, as some genes and transcription factors, like CREB, require elevated nuclear calcium for their induction [43,44]. Thus, in the first step of stimulation–transcription coupling, stimuli are translated into a temporal and spatial pattern of calcium within the neuron.

Next, temporal and spatial patterns of calcium determine signaling pathway activation. First, the temporal pattern of stimulation, together with that of the resulting calcium influx, influences the extent of phosphorylation of ERK, CaMKII, and AKT; the extent of activation of calcineurin; and the nuclear levels of NFATc3 [10••,40•,41,42,45]. Rather than influencing the extent of pathway activation, the source and cellular location of calcium affects which signaling pathways are activated. Calcium influx through NMDA receptors and L-type channels activates signaling pathways that reside near the channel, such as MAPK/ERK and CaMKII [46–50], whereas calcium released from intracellular stores activates not only MAPK/ERK but also PKC [37,51]. Furthermore, calcium influx into as few as three dendritic spines activates nuclear transport of synapse-residing signaling molecules and transcription factors, including ERK, Jacob, CRTC1, CREB2, NPAS4, and NFκB [33••,52–56], whereas other signaling molecules, such as CaMKIV, reside in the nucleus [46] and are therefore less likely to be activated by synaptic signals. Thus, spatial and temporal calcium patterns throughout the cell determine which signaling molecules reach the nucleus and their degree of activation upon arrival.

Once in the nucleus, different signaling pathways activate different transcription factors [29], and different transcription factors regulate different subsets of ARGs [57–60]. For example, MAPK/ERK signaling activates SRF [29], which binds specifically to the promoters and enhancers of the rapid genes induced by brief activity [10••], whereas MEF2 is activated by calcineurin and binds to the promoters and enhancers of a subset of genes that includes both rapid and delayed genes [10••,29]. Thus, some rapid genes are regulated by both SRF and MEF2. Such combinatorial regulation, where each gene is regulated by multiple transcription factors, allows a given gene to be transcribed in response to multiple types of stimuli. Indeed, the ARG *Fos* is regulated by five different enhancers that each bind different transcription factors and respond to different types of stimulation, including membrane depolarization, BDNF, and forskolin [61•]. Globally, different activity-regulated enhancers bind different combinations of transcription factors [62,63] and are activated to different extents in response to different durations of membrane depolarization [10••]. These global findings suggest that enhancers establish stimulation–transcription coupling by specifying which stimuli regulate each ARG.

In a final layer of coupling regulation, transcription factor binding to promoters and enhancers is often dependent on chromatin state, which differs between ARG modules before stimulation and also changes with stimulation [26,58,64–70]. The rapid genes induced by brief membrane depolarization have a relatively active, open chromatin state in unstimulated neurons [10••,71]. As chromatin remodeling takes time, these rapid genes may be primed by this open chromatin state to respond quickly to brief stimulation. In contrast, delayed genes have a relatively closed chromatin state in unstimulated neurons [10••], and their induction requires histone turnover [72•] as well as the bromodomain protein Brd4 [73], which recognizes histone acetylation. Stimulus-dependent chromatin remodeling of these delayed genes is mediated by the AP1 transcription factor complex [74•]. Thus, whether a stimulus can initiate chromatin remodeling may determine which kinetically defined gene classes it can induce.

Using stimulation–transcription coupling to infer past stimulation

The existence of a stimulation–transcription coupling map suggests that neurons encode information about their stimulation history in gene expression, that is, the set of mRNAs in the cell at any given time. Indeed, the duration of stimulation, as well as the type of psychotropic drug added to cultured neurons, can be inferred from gene expression a few hours after stimulation, formally demonstrating such encoding [10••,12,13]. This type of inference could be a powerful tool when paired with single cell RNA-seq, allowing assessment of the stimulation history of tens of thousands of neurons in a single experiment [10••].

In addition to inferring the stimulation history of individual neurons, the coupling map could also be used to infer the past experience of an animal. An experience leaves a unique ARG signature in the brain that encompasses both where in the brain ARGs are expressed [75] and which ARGs are induced [76••,77–79]. A recent study used this ARG signature to infer past experiences that included cocaine exposure and foot shock [76••]. They found that using both components of the ARG signature (which genes are induced and where) allowed better inference than using just one component. Once we better understand which ARG modules are important for which plasticities, these ARG signatures could help reveal where in the brain different forms of experience-dependent plasticity occur.

Conclusions

Genomic experiments have dramatically improved our ability to create a map of stimulation–transcription coupling. *In vitro* experiments that systematically vary a

stimulus along a single dimension of stimulation space have been, and will continue to be, helpful for describing these coupling principles. However, *in vivo*, a single stimulus can vary along multiple dimensions of stimulation space, and a neuron can receive multiple different stimuli at one time. Thus, going forward, it will be important to determine how different dimensions of stimulation interact in their coupling to transcription.

While testing all of stimulation space would be prohibitively laborious, we could instead focus on achieving a full coupling map for a single neuronal subtype, thus limiting the relevant stimulation space to only the stimuli experienced by that subtype *in vivo*. With such a map in hand, it may eventually be feasible to manipulate the coupling map, that is to change the genes induced by a given stimulation through manipulation of gene-module-specific regulation. Such a manipulation has the potential to link gene modules to physiologically relevant plasticities and to reveal new transcription-dependent mechanisms of neuronal plasticity.

Conflict of interest statement

Nothing declared.

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