atom to another internal atomic state that was resonant with the optical field inside the cavity sufficed to change the resonance wavelength of the cavity substantially and block the transmission of the source field (*5*). Thus, as soon as a single gate photon underwent a coherent scattering event in the ensemble, the cavity transmission was reduced and most of the source light incident on the cavity was reflected. In this way, the authors showed that a gate field that contained only a single photon could switch between the transmission and reflection of the source light field containing hundreds of photons.

The performance of the device even went beyond that of a classical switch operated by a single photon. As long as no information is available about which atom changed its state, quantum interference allows the coherent scattering process to be reversed. Thus, the initial gate photon could be retrieved from the atomic ensemble after blocking the transmission of the source photons. In this case, the atomic ensemble was operated as a so-called quantum memory (*2*, *3*). Here, the number of source photons that could be redirected was smaller than in this previous experiment: Because of experimental imperfections, a small fraction of the source light will still enter the cavity and can then be scattered outside of the cavity by the atom. This process will more likely occur for a larger number of incident source photons and will reveal which atom changed its state, thereby destroying the quantum interference necessary for retrieving the gate photon. Chen *et al*. found that a single gate photon that was stored in their quantum memory could redirect a source field containing up to two photons before the retrieval of the gate photon was impeded. Although this number seems small, it exceeds 1 and is above the critical threshold for a positive gain of their transistor.

With their experiment, Chen *et al*. demonstrated the feasibility of an all-optical transistor that can be triggered by only a single gate photon. That such a system can be operated in the quantum regime opens the way to future photonic devices that could be used for light-based quantum information protocols (*6*). To this end, the next critical step will be to optimize the performance of such systems, which requires enhancing the absorption probability of the gate light in the atomic ensemble. Moreover, the efficiency of coupling the source light into and out of the optical resonator will have to be improved. In independent experiments, highly efficient quantum memories (*7*) and optical resonators with coupling efficiency close to 1 (*8*, *9*) have been realized. Combining these improvements in the same system would allow the realization of an efficient all-optical transistor, which in turn might enable the implementation of deterministic quantum logical operations between individual photons (*6*)—the key element of an optical quantum computer.

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NEUROSCIENCE

Mapping Neuronal Diversity One Cell at a Time

A universal method for classifying neuronal subtypes will increase our understanding of the human brain.

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How many types of nerve cells are there in the mammalian central nervous system (CNS)? We still do not have a satisfactory answer to this deceptively simple question, and yet the precise assignment of nerve cells to well-defined subtype categories is critical both for elucidating the function of neural circuits and for the success of neural regenerative medicine. Amid the anatomical, electrophysiological, and biochemical diversity of nerve cells, the field is struggling to devise simple and clear criteria for neuronal classification. A universally applicable classification system should be based on traits that are objectively quantifiable, sufficiently diverse, and reproducible in independent laboratories. Such a classification method would provide new insights into CNS organization, development, and function, and might reveal unexpected relationships between neuronal subtypes.

To fully characterize nerve cells and appreciate their diversity, they are analyzed at all three phenotypic levels—anatomical, biochemical, and electrophysiological. Complete anatomical mapping was accomplished for the CNS of the worm *Caenorhabditis elegans* by reconstruction of serial electron micrographs (*1*). Ultrastructural mapping is complemented by analysis of anatomy and connectivity based on cell type–specific expression of reporter genes to effectively study the much larger mammalian CNS (*2*, *3*). At the biochemical level, ongoing efforts to map expression patterns of developmentally regulated genes provide fundamental insights into molecular diversity and developmental programs of individual nerve cells (*4*, *5*). And at the electrophysiological level, new research programs, such as the recently announced Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative, are supporting development of technologies for global mapping of neuronal activity in behaving animals (*6*). Although integration of the three complementary approaches is essential for the ultimate understanding of brain structure and function (*7*, *8*), at the single nerve cell level such detailed analysis poses a problem as it allows assignment of each nerve cell to multiple different subtype groups.

Currently we do not have a system to provide a definitive count of neuronal subtypes, even in a small region of the mammalian CNS. A recent review on subtype diversity of neocortical interneurons provided a partial solution by proposing to focus on a few easily distinguishable morphological phenotypes to categorize inhibitory interneurons (*9*). Although such an approach is practical and immediately applicable to classification of cortical interneurons, it is not sufficiently universal to be easily transferable to other types of neurons and might miss important

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functional differences among interneurons that are not manifested by anatomically discernible features.

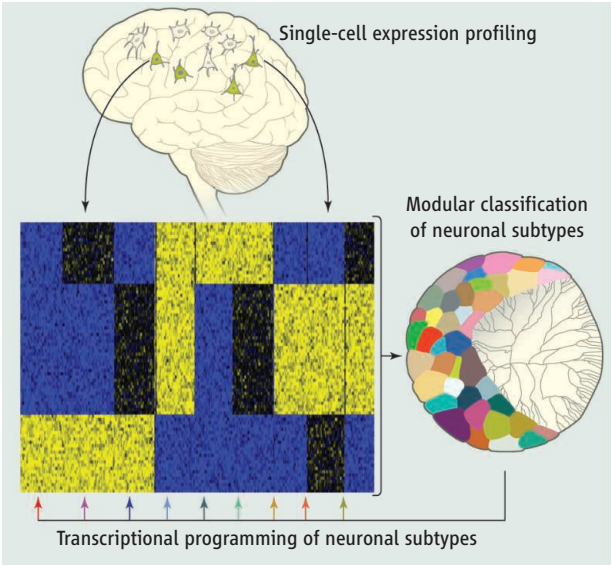
Differential expression of developmentally regulated genes determines most aspects of neuronal identity. The expressed genes not only define neuronal connectivity and physiology but also determine and reflect neuronal responses to external signals and patterns of neuronal activity. Unlike other types of phenotypic characterization (morphology or electrophysiology), gene expression provides extremely rich and diverse data sets with large numbers of measurable attributes. Advances in next-generation sequencing make analysis of global gene expression relatively easy, quantitative, and highly reproducible (*10*).

Current gene expression studies typically rely on profiling neuronal populations that have been partially purified on the basis of reporter gene expression. A systematic approach to profile all neuronal populations has been recently completed for the mouse retina (*5*). While the resulting data provide insights into the diversity of principal neuronal classes, reliance on reporter genes expressed in multiple neuronal subtypes implies that the resulting expression profiles are composites (*5*). Computational deconvolution of such complex data sets requires a priori knowledge of neuronal diversity within the sorted cell populations, thereby limiting the discovery of new neuronal subtypes (*11*).

Given the utility and generality of expression data, we propose that single-cell expression profiling be used to characterize neuronal diversity (see the figure) (*12*). Single-cell RNA sequencing (RNA-seq) provides an unbiased and systematic method of "fingerprinting" an aspect of cellular state that enables similar cells to be computationally identified (*13*). However, several challenges need to be overcome to ensure the success of this approach. One is that universally adoptable protocols that yield consistent data in different laboratories will need to be developed, so that data can be progressively built into a universal "neuronal gene expression reference library" (*4*).

Another challenge will be to devise strategies for assigning expression profiles to discrete subtype categories. Computational methods could determine the degree of similarity between individual profiles and draw subtype boundaries between groups of cells. For example, existing algorithms for high-dimensional single-cell cytometry data arrange cells in a branched tree structure defining their relatedness (*14*). Once subtype identities are determined, it will be possible to extract a core set of differentially expressed genes defining neuronal subtype identity (subtype signature). The flexibility of this system will make it easy to continuously add expression profiles, update models, and define finer neuronal subtype categories.

Relating the expression signatures to nerve cell function will also be key to the success of this approach. Focused analysis of neuronal subsets based on reporter expression will decrease the cellular complexity of studied samples and provide a link between expression profiles and functional attributes derived from parallel morphological and electrophysiological studies. Some neuronal phenotypes such as the neurotransmitter and electrophysiological properties will correlate with expression of core signature genes encoding enzymes involved in neurotransmitter biosynthetic pathways, and receptors and ion channels defining neuronal membrane properties (*15*, *16*). Other phenotypes such as position within the CNS, morphology of the cell, or connectivity might be harder to correlate with expression profiles as these phenotypes are controlled by programs active during neuronal development. Whether a footprint of these developmental programs is carried over into the terminal neuronal signature remains to be determined.



Classifying neuronal subtypes. Clustering of single-cell expression profiles provides an objective method for subtype classification. Regulatory relationships between genes can be computationally extracted from the expression profiles, defining sets of transcription factors (TFs) critical for the establishment and maintenance of subtype-specific expression profiles. Discovered transcription factor modules can be used to reprogram other cell types to desirable neuronal subtypes.

Single-cell RNA-seq data for classifying neuronal subtypes will have additional applications. For example, correlation of differentially expressed genes with connectivity and electrophysiology might decipher effects of neuronal activity, cell signaling, and memory formation on neuronal transcriptomes. The discovered molecular signatures might provide novel insights and tools for studying CNS function.

Another area that will benefit from the expression data is transcriptional programming of neuronal identity. Programming factors are typically discovered by a tedious trial-and-error method, and their ability to program functional nerve cells matching their in vivo counterparts is frequently questioned. Cross-referencing expression profiles of programmed cells with the neuronal reference expression library will provide an unambiguous measure of the quality and subtype identity of programmed cells. Furthermore, RNA-seq data can be used to estimate transcriptional networks and to predict key transcription factors controlling subtype-specific expression profiles (*17*). Such prospectively identified transcription factors, capable of programming neuronal subtype identity in diverse cellular contexts, will have a practical impact on production of specific nerve cells either from pluripotent stem cells in vitro or by reprogramming endogenous neural stem cells in vivo. Effective and subtype-specific neuronal programming might find application in cell replacement therapies or for modeling neurodegenerative diseases in vitro.

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