

A transcriptional signature of hub connectivity in the mouse connectome

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Connectivity is not distributed evenly throughout the brain. Instead, it is concentrated on a small number of highly connected neural elements that act as network hubs. Across different species and measurement scales, these hubs show dense interconnectivity, forming a core or “rich club” that integrates information across anatomically distributed neural systems. Here, we show that projections between connectivity hubs of the mouse brain are both central (i.e., they play an important role in neural communication) and costly (i.e., they extend over long anatomical distances) aspects of network organization that carry a distinctive genetic signature. Analyzing the neuronal connectivity of 213 brain regions and the transcriptional coupling, across 17,642 genes, between each pair of regions, we find that coupling is highest for pairs of connected hubs, intermediate for links between hubs and nonhubs, and lowest for connected pairs of nonhubs. The high transcriptional coupling associated with hub connectivity is driven by genes regulating the oxidative synthesis and metabolism of ATP—the primary energetic currency of neuronal communication. This genetic signature contrasts that identified for neuronal connectivity in general, which is driven by genes regulating neuronal, synaptic, and axonal structure and function. Our findings establish a direct link between molecular function and the large-scale topology of neuronal connectivity, showing that brain hubs display a tight coordination of gene expression, often over long anatomical distances, that is intimately related to the metabolic requirements of these highly active network elements.

connectome | complex networks | hub | rich club | metabolism

Certain neural elements possess an unusually high degree of connectivity, designating them as putative network hubs (1). Analyses of microscale, mesoscale, and macroscale connectomes of multiple species, constructed using a variety of methods, indicate that these hubs are strongly interconnected with each other, forming a so-called “rich club” of connectivity that mediates a large fraction of communication traffic in the brain and supports the efficient integration of otherwise segregated neural systems (2–8).

Hub connectivity is functionally advantageous, but it is also costly. Hub regions make more connections with other areas, and these connections often extend over long anatomical distances, thus requiring greater physical space, cellular material, and metabolic resources (3, 9). Accordingly, human neuroimaging studies have indicated that topologically central hub regions have a higher energetic demand than other brain areas (9–12), which may render them particularly vulnerable to the effects of damage or disease (10, 13). This hypothesis is supported by evidence that pathology in a broad range of disorders preferentially accumulates within highly connected brain regions (14).

Hub connectivity is thus a topologically central and costly aspect of brain network organization that is conserved across species and spatial scales. This conservation suggests that hub connectivity may be under tight genetic control. Growing evidence indicates that gene expression affects neuronal connectivity, with studies of worm, rat, and mouse nervous systems showing that the transcriptional profile of an individual neuron or neuronal population can predict its connectivity to other areas with greater than chance accuracy (15–19). Brain regions with similar transcriptional profiles

display similar connectivity profiles (20, 21), and gene expression profiles are more correlated between pairs of structurally connected brain regions in the mouse/rat (20) and within functionally coupled networks of the human cortex (22). Functional neuroimaging of human twins indicates that the topological properties of hub connections are strongly heritable (23), but it is not known whether the topologically distinctive and functionally important connections between hub regions are associated with a unique transcriptional signature. Characterizing this relationship is critical for understanding the molecular basis of topological specialization in brain networks.

In this work, we show that the topologically central and costly connections involving hubs of the mouse brain are associated with a distinct transcriptional signature. Transcriptional coupling is greatest for pairs of connected hubs, intermediate for connections between hubs and nonhubs, and lowest for connected pairs of nonhubs, a trend that mirrors the signaling load that these connections are likely to carry (3, 4). The highly correlated gene expression profiles of connected hubs are not driven by the coupling of genes associated with structural connectivity in general (which we show are involved in neuronal connectivity and communication) but are driven by genes regulating oxidative metabolism. We thus identify a close interplay between gene transcription and large-scale brain network architecture and show that the primary genetic distinction between different classes of neuronal connections is intimately related to the metabolic demand of the regions that they interconnect.

Topological Centrality and Cost of Hub Connectivity

We first describe the topological properties of the mouse connectome from work by Oh et al. (24), represented here as a binary,

Significance

Some brain regions are highly connected with other areas, designating them as network hubs. These hubs are also heavily interconnected with each other, forming a dense core that integrates information across different neural systems. Here, we show that the functionally important projections linking hub areas of the mouse brain have a distinct genetic signature that is characterized by the tightly coupled expression of genes regulating the synthesis and metabolism of ATP, the primary energy source for neural activity. Our findings establish a direct link between molecular function and the large-scale organization of neuronal connectivity and suggest that coordinated gene expression between hub areas is closely related to the metabolic demands of these highly active and functionally important regions.

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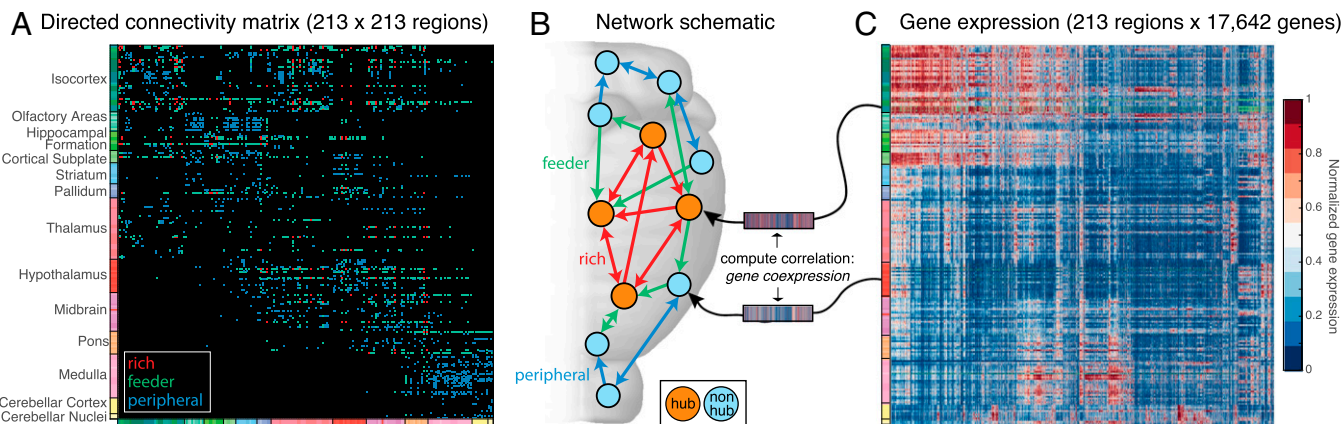


Fig. 1. Mapping the transcriptional signature of large-scale brain network topology. (A) Defining highly connected hub regions with connectivity degree $k > 44$, all neuronal connections between each of 213 brain regions were labeled as rich (hub → hub; red), feeder (hub → nonhub or nonhub → hub; green), or peripheral (nonhub → nonhub; blue). (B) Network schematic illustrating the different connection types in the mouse brain. (C) Normalized expression levels of 17,642 genes (columns) measured in each brain region (rows) visualized here using color from low (blue) to high (red) are used to compute the correlation in expression profiles or gene coexpression for each pair of brain regions. Missing data are shown as green, and columns of the matrix have been reordered using hierarchical clustering to place genes with correlated expression patterns close to one another.

directed adjacency matrix that encodes 3,063 anatomical connections between 213 brain regions in the right hemisphere (Fig. 1A). The total number of connections involving a given brain region is called its degree, k . The distribution of k across all regions of the mouse connectome, plotted in Fig. 2A, reveals an extended tail of highly connected hub regions. For each value of k , we quantified the tendency of nodes with degree $> k$ to preferentially connect to each other, forming a rich club, using the normalized rich club coefficient, $\Phi_{\text{norm}}(k)$. Values of $\Phi_{\text{norm}}(k) > 1$ indicate rich club organization of the network (7, 25). As shown in Fig. 2B, the mouse connectome displays rich club organization across the contiguous range $42 \leq k \leq 54$ ($P < 0.05$, shaded gray area in Fig. 2B), reflecting dense connectivity between these high-degree hub regions. This range of k is referred to as the “topological rich club regime” throughout this work.

Putative hub regions are distributed broadly across anatomical brain divisions in the topological rich club regime (Fig. S1B). For example, hubs with $k > 42$ are present in 9 of 13 broad anatomical divisions of the Allen Mouse Brain Atlas (24, 26). Relative to other types of network connections, connections between hubs show a greater mean connection distance (Fig. 2B), an increased proportion of reciprocal connections (Fig. S1D), and higher average connectivity weight (Fig. S1E). The high density, reciprocity, connection weight, and connection distance of hub–hub connections characterize the high-topological wiring cost of these links (3, 9, 10). These findings counter the general trend across the brain, where the probability of a connection between two brain areas decays exponentially with their physical separation, as does the probability that a connection will be reciprocal (Fig. S2). Hub–hub connections also play a topologically central role in network communication, as measured by their edge betweenness centrality and network communicability (Fig. S1F), suggesting that they are well-positioned to mediate a large proportion of signal traffic in the mouse brain. All of the above-mentioned properties of hub–hub connections display a similar increasing trend with k and a significant increase relative to all other connections across the topological rich club regime ($P < 0.05$). Thus, hubs of the mouse connectome are distributed broadly across anatomical divisions and show a rich club organization characterized by a high wiring cost and topological centrality, consistent with prior observations in other diverse species (2–7).

Gene Coexpression and Neuronal Connectivity

We next investigated how the connectivity of pairs of regions of the mouse brain relate to their transcriptional coupling, as illustrated

in Fig. 1. Transcriptional data for 17,642 genes were obtained from the Allen Mouse Brain Atlas (26) and normalized across the brain for each gene, yielding an expression profile for each brain region (Fig. 1C, rows). To compare different classes of pairwise connections, we examined patterns of gene coexpression (transcriptional coupling) measured for each pair of brain regions as the Pearson correlation of their expression profiles. Gene coexpression values were corrected for strong spatial correlations in the data (Fig. S3), ensuring that our results reflect robust effects of connectivity and connection topology that cannot be explained simply by the spatial proximity of different pairs of brain regions (Materials and Methods).

We investigated the relationship between gene coexpression and neuronal connectivity by comparing three different classes of brain region pairs, i and j (excluding self-connections): (i) reciprocally connected ($i \leftrightarrow j$), (ii) unidirectionally connected ($i \rightarrow j$ or $j \rightarrow i$, but not both), and (iii) unconnected. Spatially corrected gene coexpression is greatest in reciprocally connected pairs of brain regions (mean \pm SD = 0.10 ± 0.17) followed by unidirectionally connected pairs (0.06 ± 0.16) and lowest in unconnected

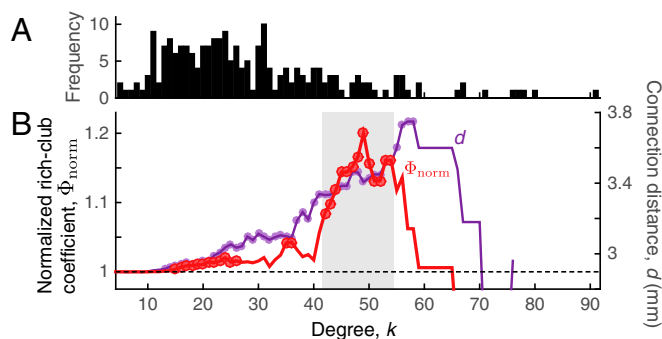


Fig. 2. The mouse connectome contains a costly and topologically central rich club of densely interconnected hub regions. (A) Degree distribution of the mouse connectome. (B) Normalized rich club coefficient, Φ_{norm} (red), and mean connection distance, d , of hub–hub links (purple) as a function of the degree, k , at which hubs (regions with degree $> k$) are defined. Red circles indicate values of Φ_{norm} that are significantly higher than an ensemble of 10,000 null networks (permutation test; $P < 0.05$); purple circles indicate where the mean connection distance of hub–hub links is significantly increased relative to all other network links (one-sided Welch's t test; $P < 0.05$). The topological rich regime ($42 \leq k \leq 54$) is shaded gray.

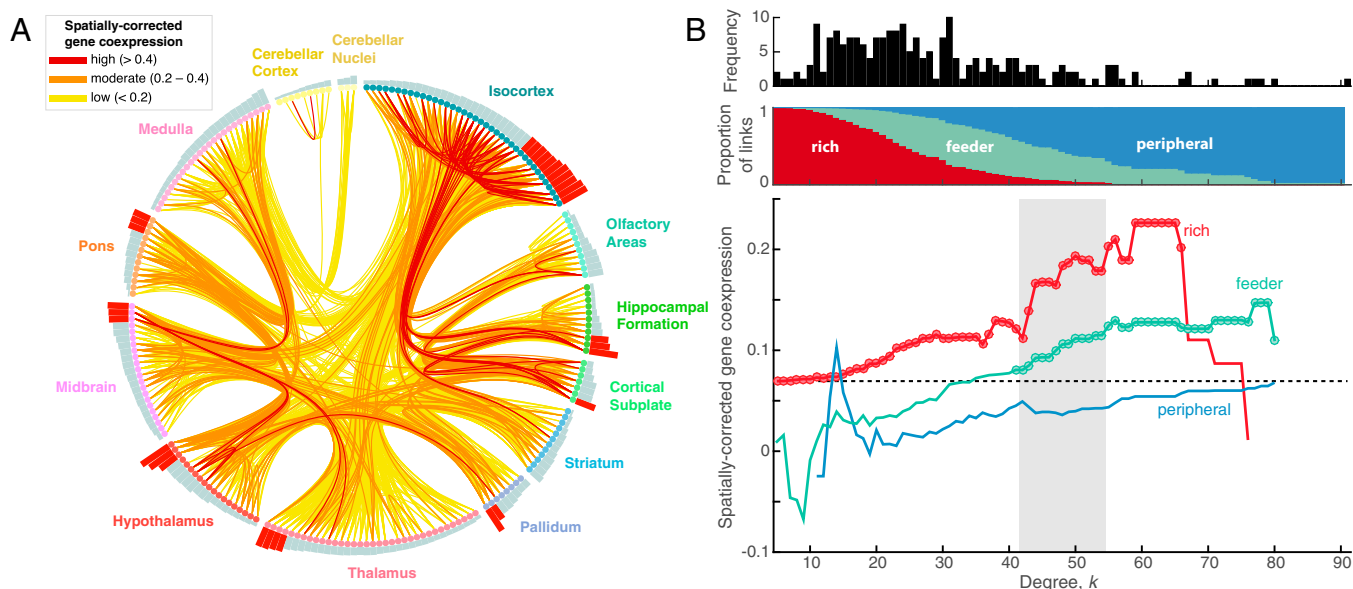


Fig. 3. Gene coexpression is elevated for connections involving brain network hubs. (A) Connectogram showing (spatially corrected) gene coexpression values across the mouse connectome. All neuronal connections (lines) between brain regions (circles) are colored according to the gene coexpression of the regions that they connect. Brain regions are organized by anatomical division and sorted by degree (shown as bars), with bars colored bright red for hubs ($k > 44$). A larger version of this connectogram with all regions labeled is in Fig. S4. (B, Top) Degree distribution. (B, Middle) Proportion of links classified as rich, feeder, and peripheral, where hub nodes have degree $> k$. (B, Bottom) Mean (spatially corrected) gene coexpression for rich, feeder, and peripheral connections as a function of k , with the mean across all network links shown as a dashed black line and the topological rich club regime shaded. Circles indicate a statistically significant increase in gene coexpression in a given link type relative to the rest of the network (one-sided Welch's t test; $P < 0.05$).

pairs (-0.01 ± 0.16 ; all differences are statistically significant; Welch's t test, $P < 10^{-6}$) (Fig. S3C).

To investigate which functional groups of genes contributed to this trend in transcriptional coupling, we developed a measure that quantifies the contribution of each gene to the overall correlation in expression levels between pairs of brain regions, referred to here as the gene coexpression contribution (GCC) score. These GCC scores were then used to perform a gene function analysis (Materials and Methods). At a false discovery rate of 0.05, 31 distinct functional groups of genes [using Gene Ontology (GO) annotations for biological processes (27)] show a significantly increased contribution to gene coexpression for connected pairs of brain regions relative to unconnected pairs ($P < 0.05$) (Table S1). The majority of these GO categories are related to neuronal connectivity and communication, including genes regulating synapse structure, function, and plasticity; neuronal membrane potentials; neurotransmitter signaling; dendritic spine morphogenesis; and axonogenesis. Similar categories were also selected when cellular components were included in the analysis (Table S2). Other categories are related to metabolism, such as those involved in the electron transport chain and mitochondrial function, suggesting an increased energy demand for connected pairs of brain regions over unconnected pairs, likely reflecting the metabolic cost of neuronal communication (28). Similar GO categories related to neuronal communication and connectivity were obtained when comparing separately (i) reciprocal vs. unconnected pairs and (ii) unidirectional vs. unconnected pairs, indicating a robust transcriptional signature of structural connectivity in the mouse brain that varies quantitatively (rather than qualitatively) as a function of connection presence and reciprocity.

Gene Coexpression and Hub Connectivity

Having characterized a distinctive transcriptional signature of neuronal connectivity in the mouse brain, we next investigated whether gene coexpression might also vary as a function of connection type, focusing particularly on different classes of connections

involving hubs (Fig. 1B). At each k , we labeled each brain region as either a hub (nodes with degree $> k$) or a nonhub (otherwise), and then labeled each connection as rich (hub \rightarrow hub), feeder (nonhub \rightarrow hub or hub \rightarrow nonhub), or peripheral (nonhub \rightarrow nonhub) (3). The anatomical distribution of hubs, interregional connections, and gene coexpression values is shown in Fig. S4.

Across the topological rich club regime, mean gene coexpression is significantly increased for connections involving hubs (i.e., rich and feeder connections) and is greatest for rich connections (Fig. 3B). Mean gene coexpression of rich connections increases sharply at the start of the topological rich club regime ($k = 42$) and continues to increase with k , indicating that transcriptional coupling is strongest for pairs of the most highly connected hubs. Across the topological rich club regime, gene coexpression is significantly greater in (i) rich links than feeder links and (ii) feeder links than peripheral links (Welch's t test; all $P < 0.01$). For example, at $k = 42$, (spatially corrected) gene coexpression is greatest for rich links (mean \pm SD = 0.11 ± 0.17) followed by feeder links (0.08 ± 0.17) and peripheral links (0.05 ± 0.16). This same increase in gene coexpression for rich connections was reproduced using a range of different data processing methods [including variations in connectome density (Fig. S5) and spatial correction procedures (Fig. S6)], highlighting the robustness of this result.

To determine whether specific functional groups of genes drive this correlated gene expression signature of hub connectivity, we used our method of assigning GCC values to genes to compare connections involving hubs with peripheral connections between nonhubs (Materials and Methods). Hubs were defined as brain regions with $k > 44$, corresponding to 1 SD above the mean of the degree distribution (1, 7) (Table S3). The five biological process GO categories that show a significant increase in gene coexpression in rich and feeder connections over peripheral connections ($P < 0.05$) fall into two parent categories related to oxidative energy metabolism: (i) hydrogen ion transmembrane transport and (ii) citrate metabolic process (Table 1). When GO annotations for cellular components were also included in the

GO category	P value
Hydrogen ion transmembrane transport	0.04
Energy-coupled proton transmembrane transport against electrochemical gradient	0.0097
ATP hydrolysis-coupled proton transport	0.0097
Citrate metabolic process	0.045
Tricarboxylic acid cycle	0.014

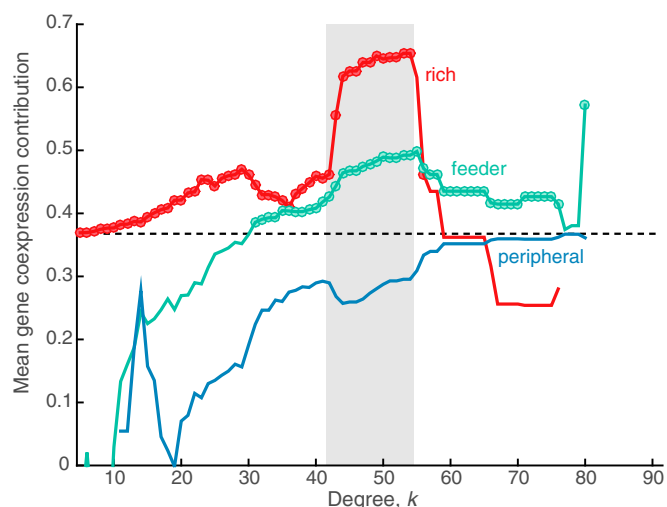
analysis, in total, 25 functional groups of genes were selected ($P < 0.05$), including mitochondrial respiration, cellular respiration, mitochondrial membrane, and proton-transporting ATPase complex (Table S4). Importantly, similar functional groups of genes drive the increased transcriptional coupling of both (i) rich links compared with peripheral links and (ii) feeder links compared with peripheral links (Table S5), pointing to a robust and consistent transcriptional signature of connections involving hubs.

Discussion

Gene Coexpression and Neuronal Connectivity. The idea that connected neural elements should show coupled molecular function was suggested in the work of Ramón y Cajal (29) and later elaborated in Sperry's chemoaffinity hypothesis for how developing neural connections find their targets (30). Developmental processes involved in establishing and maintaining neuronal connectivity, such as neurite outgrowth and guidance, synapse formation, and synaptic transmission, are all under tight transcriptional regulation (31). We should therefore expect that genes involved

Our findings, obtained using a novel methodology to combine connectivity and expression data, support this view. For both reciprocal and unidirectional connections, correlated gene expression is driven by the same types of functional gene groups, pointing to a uniform transcriptional profile of connectivity that increases with connection reciprocity. Similar functional categories of genes related to the development of neurons, neurites, and synapses, as well as the regulation of neuronal activity and synaptic plasticity, contribute to predicting the presence of a connection between neurons in *Caenorhabditis elegans* (15, 16) and larger-scale neuronal populations of the rat (17) and mouse brains (18, 19). The consistency of these findings across species, datasets, and analysis methods points to a robust transcriptional signature of neuronal connectivity characterized by the coordinated expression of genes involved in the development and ongoing function of neuronal networks.

The high wiring cost of hub connectivity is coupled with an increased demand for metabolic resources (9–12). Our results



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indicate that this demand defines the transcriptional signature of hub connectivity. Specifically, we report that gene coexpression is highest for rich connections (pairs of connected hubs) followed by feeder connections (connected hubs and nonhubs), with both rich and feeder connections showing significantly increased gene coexpression relative to peripheral connections (pairs of connected nonhubs). This result is robust to variations in processing and analysis procedures (Figs. S5 and S6) and is striking when one considers the broad anatomical distribution and functional diversity of hubs (Fig. 3A). Indeed, the strong transcriptional coupling of connections involving hubs persists despite spanning distinct neural systems and extending over long anatomical distances. Importantly, the same types of functional gene groups involved in oxidative metabolism drive the increase in gene coexpression for both rich and feeder connections relative to peripheral connections, indicating that the transcriptional distinction between rich and feeder connections is quantitative rather than qualitative. The increasing gradient of gene coexpression from peripheral to feeder to rich links follows the expected signal traffic that these different connection classes are thought to mediate, as indicated by both topological analysis (3) and computational models of interregional communication (4). This convergence suggests that the transcriptional signature of different types of interregional connections may be determined by the metabolic resources required to meet their differential signaling load, consistent with evidence that the energetic requirements of neuronal signaling scale with action potential frequency (28).

Genes driving the correlated gene expression signature of hub connectivity are involved in the synthesis and breakdown of ATP. Increased transcriptional coupling of these genes was highly specific to rich and feeder connections across the topological rich-club regime of the mouse connectome. ATP is the energetic currency of neuronal signaling (28) and is predominantly supplied by oxidative phosphorylation, with ~10–12% of energy supplied by nonoxidative metabolism in the form of aerobic glycolysis (33). Human functional and metabolic imaging has shown that brain regions with high-degree and topological centrality consume more glucose (12) and have higher regional blood flow (11) and glycolytic activity (9, 10) than other areas, suggesting a role for both oxidative and nonoxidative pathways in meeting the energetic requirements of hub areas.

Our findings emphasize the role of oxidative phosphorylation in supporting high-cost communication between hub areas. Functional groups of genes showing elevated coexpression for rich and feeder connections (Table 1) include nine genes encoding different subunits of the mitochondrial *H⁺-ATP synthase subunit 5*, which catalyzes ATP synthesis by oxidative phosphorylation, as well as four genes encoding subunits of cytochrome oxidase c, which is the terminal enzyme in the mitochondrial electron transport chain and which has activity levels that are tightly coupled with neuronal signaling (34). The categories also include a cluster of genes coding proteins involved in citrate metabolism (*Sdh*, *Mdh*, *Idh*, and *Pdh*). Notably, *Pdh* acts as a molecular bridge between glycolysis and oxidative phosphorylation by catalyzing the conversion of pyruvate to acetyl-CoA, further underlining the role of oxidative metabolism in the transcriptional signature of hub connectivity.

Our analysis of the adult mouse brain reflects the functional requirements of supporting neuronal connectivity in a mature neural system. Although many aspects of gene expression in the brain show a developmentally persistent profile (35), it is unclear whether the same transcriptional signature of hub connectivity

would be apparent throughout development. Although rich club connectivity seems to be established early in development (2, 36), it also undergoes significant remodeling later in life (37). Interestingly, recent evidence indicates that aerobic glycolysis plays a prominent role in biosynthesis and growth and that it accounts for a larger fraction of the brain's energetic needs earlier in development, peaking in early childhood when levels of synaptic development are highest (35). This work also found that areas of the adult human brain with high levels of glycolytic activity show increased expression of genes regulating synapse formation and growth, whereas brain regions with high glucose metabolism show elevated expression of genes regulating mitochondria and synaptic transmission (35). Collectively, these findings suggest that the development and remodeling of synaptic networks is associated with the expression of genes regulating aerobic glycolysis. On the other hand, signaling across established or mature networks, particularly along links involving hub nodes, may be supported by the coordinated expression of genes regulating oxidative phosphorylation.

Implications for Disease. Many complex diseases of the brain can be construed as disorders of neuronal connectivity, and the high metabolic demand of hub regions may render these areas particularly vulnerable to the effects of injury or disease (10, 13, 14, 38). It is well-known that metabolic abnormalities (mitochondrial dysfunction in particular) play a key role in the pathophysiology of many neurological disorders, including Alzheimer's and Parkinson's diseases (38–41), schizophrenia (42), and others. Although the exact causes of these disorders are no doubt complex, our results point to a close interplay between the topological organization of hub connections and the transcription of metabolic genes. This link suggests that a closer investigation of how brain network topology relates to the energetic requirements of neuronal signaling may help elucidate the pathogenesis of these disorders.

Materials and Methods

A summary of our analysis methods is provided here, with additional detail provided in *SI Materials and Methods*. Mouse brain connectivity data were obtained from the Allen Mouse Brain Connectivity Atlas (24), and expression data were obtained from the Allen Mouse Brain Atlas (26). Because the magnitudes of in situ hybridization-measured expression levels are not directly comparable across genes (43), they were normalized across the brain for each gene using a scaled sigmoidal transformation. This choice of normalization did not drive our qualitative results, which were reproduced using a range of normalizing transformations (*SI Materials and Methods*). The gene coexpression value for a pair of brain regions is defined as the Pearson correlation between the normalized expression levels across all genes. Gene coexpression values display strong spatial correlations that decay exponentially with separation distance (Fig. S3B). We corrected for this exponential trend, analyzing spatially corrected gene coexpression data as the residuals of an exponential fit to the data. This correction allowed us to analyze patterns of gene coexpression beyond what would be expected purely based on the spatial proximity of brain regions. The contribution of each individual gene to the spatially corrected gene coexpression value for each interregion pair was measured as a GCC score using the definition of the Pearson correlation. Each gene was assigned a *t* statistic measuring the increase in GCC values (and thus, a more correlated pattern of gene expression) in one class of interregion pairs over another. Gene function analysis was performed as a gene score resampling analysis on these *t* statistics using ermineJ (44).

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