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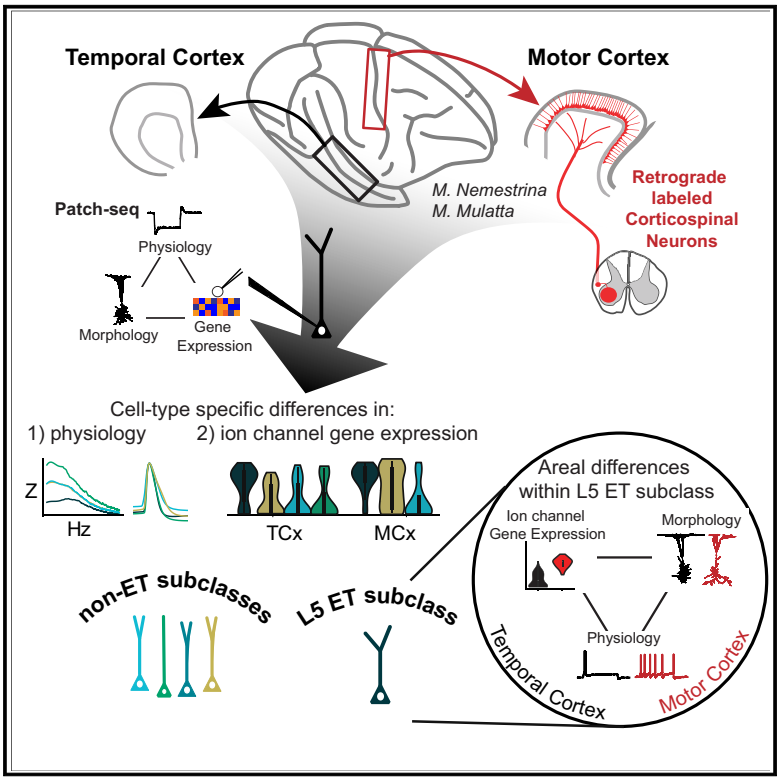
Areal specializations in the morpho-electric and transcriptomic properties of primate layer 5 extratelencephalic projection neurons

Graphical abstract



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In brief

Using Patch-seq recordings of macaque infragranular pyramidal neurons, including retrogradely labeled corticospinal neurons, Dembrow et al. identify cell-type and areal differences in gene expression, morphology, and physiology. These data demonstrate that regional specializations in function and cytoarchitecture are accompanied by differences in the intrinsic properties of discrete cell types.

Highlights

- Transcriptomically defined L5 ET neurons project subcerebrally in macaques
- Ion channel gene expression differentiates neuronal subclasses and neocortical areas
- L5 ET versus non-ET neuron physiological differences are conserved across regions
- Many cross-areal differences in L5 ET morpho-electric properties exist in macaques

Dembrow et al., 2024, Cell Reports *43*, 114718
September 24, 2024
https://doi.org/10.1016/j.celrep.2024.114718

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Areal specializations in the morpho-electric and transcriptomic properties of primate layer 5 extratelencephalic projection neurons

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https://doi.org/10.1016/j.celrep.2024.114718

SUMMARY

Large-scale analysis of single-cell gene expression has revealed transcriptomically defined cell subclasses present throughout the primate neocortex with gene expression profiles that differ depending upon neocortical region. Here, we test whether the interareal differences in gene expression translate to regional specializations in the physiology and morphology of infragranular glutamatergic neurons by performing Patch-seq experiments in brain slices from the temporal cortex (TCx) and motor cortex (MCx) of the macaque. We confirm that transcriptomically defined extratelencephalically projecting neurons of layer 5 (L5 ET neurons) include retrogradely labeled corticospinal neurons in the MCx and find multiple physiological properties and ion channel genes that distinguish L5 ET from non-ET neurons in both areas. Additionally, while infragranular ET and non-ET neurons retain distinct neuronal properties across multiple regions, there are regional morpho-electric and gene expression specializations in the L5 ET subclass, providing mechanistic insights into the specialized functional architecture of the primate neocortex.

INTRODUCTION

The neocortex is organized into specialized areas, defined by differences in cytoarchitecture and intrinsic/extrinsic connectivity.[1,2] Regional architectonic differences are enhanced in primates and are often assumed to be causally related to differences in function.[3–5] Less is known regarding the composition of neocortical circuits at the resolution of neuron types and how they vary across regions. It remains unclear whether functionally related properties, like intrinsic physiology and dendritic morphology, vary between areas for the same cell types. Striking cross-areal differences exist in the morpho-electric properties between supragranular pyramidal neurons in the primate brain,[6–8] but it is unclear whether these differences reflect regional specializations within a single neuronal subclass or different neuronal subclasses. Part of the challenge in this regard has been to comprehensively identify cell types for each region to enable rigorous comparisons across regions.

Single-cell RNA sequencing (scRNA-seq) or single-nucleus RNA sequencing (snRNA-seq) techniques have been crucial in bounding the problem of cellular diversity in the mammalian brain through the construction of transcriptomically defined cell type taxonomies in which related cell types group into subclasses that are conserved between human, non-human primate species, and mouse.[9,10] These subclasses are shared across neocortical areas, albeit at different relative abundances,[11–13] and exhibit substantial regional variation in gene expression within a single subclass.[12] Whether any one subclass exhibits phenotypic variation between areas remains largely untested in primates. Such data may provide critical mechanistic insights into the cell-type-specific and regional susceptibility to neurodegenerative disorders. Using the Patch-seq technique,[14–16] which combines scRNA-seq with patch-clamp recordings in living brain slices, phenotypic distinctions between transcriptomically defined cell types/subclasses within a neocortical area have been identified.[17–22] However, with few exceptions in the mouse neocortex,[23] whether such distinctions are conserved across neocortical areas remains largely untested.

To gain insight into cross-areal variation in transcriptomic cell type cellular properties, we focused on the extratelencephalically