Structural and functional evidence supports re-defining mouse higher order visual areas into a single area V2

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Abstract:
The mouse has become one of the main organisms for studies of the visual system. As a result, there is increased effort to understand universal principles of visual processing by comparing the mouse visual system to that of other species. In primates and other well-studied species including cats and tree shrews, the visual cortex is parcellated into an area V1 and several higher order areas defined by structural and functional differences, and a near complete map of the visual field. In mice, the visual cortex beyond V1 is parcellated into several higher order areas, with less notable structural and functional differences, partial coverage of the visual field, and areal boundaries defined by reversals in progression of the visual field. Notably, recent work in tree shrews and primates has shown that reversals in progression of the visual field can be a hallmark of nonlinear retinotopic mapping within a single visual area. This, and other lines of evidence discussed here, provides a compelling case that the apparent existence of multiple higher order visual areas in the mouse is related to the false assumption of linear retinotopy. Specifically, we use simulations to show that nonlinear retinotopy within a single visual area can recapitulate the appearance of multiple areal borders beyond mouse V1. In addition, we show that many reported differences in functional properties between higher order visual areas can be better explained by retinotopic differences rather than areal identity. Our proposal to reclassify some of the higher order visual areas in the mouse into a single area V2 is not mere semantics because areal definitions influence experimental design and data analysis. Furthermore, such a reclassification would produce a common set of rules for defining areal boundaries among mammals and would bring the mouse visual system into agreement with evolutionary evidence for a single area V2 in related lineages.

Beyond V1, the mouse visual cortex has recently been parcellated into many higher order visual areas (Fig 1A). These modern area delineations are largely based on anatomical (Wang & Burkhalter, 2007) and functional (Garrett et al., 2014; Kalatsky & Stryker, 2003; Zhuang et al., 2017) signatures of a reversal in the progression of the visual field (Fig 1A). Such reversals, also known as mirror maps, indicate a new map of the visual field, and therefore a new visual area, under the assumption of simple and linear retinotopic mapping. However, recent work (Sedigh-Sarvestani et al., 2021; Yu, Rowley et al., 2020) has shown that visual field reversals are a hallmark of nonlinear retinotopic mapping within V2 and other higher order visual areas of primates and tree shrews (Fig 1B). This prompted us to ask whether the higher order areas of the mouse, delineated by reversals, may in fact be a single area V2 (Fig 1C). This would explain the partial visual field coverage of higher order areas in the mouse (Fig 1A, Zhuang et al., 2017), which only when combined provide near-full coverage of the visual field.

The parcellation of higher order visual cortex in the mouse has a contentious history (Glickfeld & Olsen, 2017) with different studies parcellating the cortex beyond V1 into between 2 (Rose, 1929) and 16 areas (Zhuang et al., 2017). Many of these studies determine areal boundaries largely based on the projection pattern of V1 terminals in higher order visual cortex. Under the assumption of linear one-to-one mapping, each point in V1 should send projections to only one point in a higher order visual areas. Therefore, the presence of multiple segregated projection terminals suggests the presences of multiple higher order visual areas (Wang and Burkhalter, 2007), but this relationship does not hold if the retinotopic map beyond V1 is nonlinear (Sedigh-Sarvestani et al., 2021; Yu et al., 2020). However, the linearity of retinotopic mapping beyond V1 in the mouse has not been investigated, which leads us to consider the areal definitions with skepticism. We are not the first to raise caution regarding this definition. Kaas et al. (1989) argued for a simple higher order cortex with repeated modules within a single area V2. Rosa and Krubitzer (Rosa & Krubitzer, 1999) used comparative anatomical analyses to argue that the presence of multiple visual areas beyond V1 “is not supported by studies of the organization of extrastriate cortex in other mammals, nor by the variability in this organization among extant rodents.” Their words of caution did not impact the next two decades of research into the organization of mouse visual cortex, in part due to the strength of anatomical tracer injections showing multiple visual field reversals beyond V1 (Wang and Burkhalter, 2007), as well as the assumption that retinotopic maps are linear and do not exhibit reversals within a single visual area. In the past decade, we have gained a better understanding of the diversity of retinotopic transformations in visual areas. Specifically, we have gained structural and functional evidence that visual field reversals can occur in single visual areas when the retinotopic transform within that area is nonlinear. These reversals, and the underlying nonlinear retinotopy, can be explained by wiring minimization principles related to visual field coverage constrained by the anatomy of cortex beyond V1, and have now been reported in tree shrews (Sedigh-Sarvestani et al., 2021), marmosets (Yu et al., 2020), ferrets (Manger et al., 2002) and squirrels (Gould III, 1984). Therefore, it stands to reason that the mouse visual system could also exhibit nonlinear retinotopic mapping beyond V1, resulting in the false appearance of multiple visual areas, where only a single unified area V2 exists.

However, if there is only a single area beyond V1 in the mouse, how can we explain the observed functional differences reported between the higher order visual areas? These include differences, varying smoothly across all higher order areas, in spectral sensitivity (Denman et al., 2018; Rhim et al., 2017), temporal and spatial frequency preferences (Han et al., 2022; Marshel et al., 2011), receptive field size, latency, binocular disparity and several other features. The simplest explanation is that these functional differences are reflective of the different visual field bias of each area (Sedigh-Sarvestani & Fitzpatrick, 2022). For instance, we would expect differences in spatiotemporal frequency and receptive field size between area RL and P, simply due to their bias towards lower central and upper peripheral parts of the visual field, which can be cone or rod-driven depending on experimental conditions.

Here we use computational models and a survey of published studies to test the hypothesis that many higher order visual areas beyond V1 can be unified into a single area V2. Specifically, we wondered a) whether published data supports the existence of a nonlinear retinotopic transform beyond V1 and b) what accounts for

the observed functional property differences among higher order visual areas as currently defined. We show that simple wiring minimization rules that explain the simple linear retinotopic maps in mouse V1 can be used to explain a complex nonlinear map beyond V1, belonging to a single secondary area. We also show that the reported functional property differences among higher order areas can be better explained by their visual field bias. More broadly, we find that many differences attributed to distinct areas can be better explained by a single area V2 if one considers two simple facts: visual field reversals are possible under nonlinear retinotopic maps and 2) functional differences exist along the gradient of eccentricity within the same visual area.

The proposed re-unification of the mouse higher order visual areas into a single area V2 would result in similar rules used to define higher order visual areas across a large array of mammals and marsupials. In addition, the existence of a single area V2 in mice would make the visual cortex of this species consistent with other rodents, and mammals, who exhibit a single area V2 beyond V1 (Rosa & Krubitzer, 1999). As it stands, the current definition of visual areas in the mouse makes the organization of visual cortex in this species distinct from nearly all other studied mammals (Fig 1C), questioning the generalizability and translational potential of findings in the mouse.

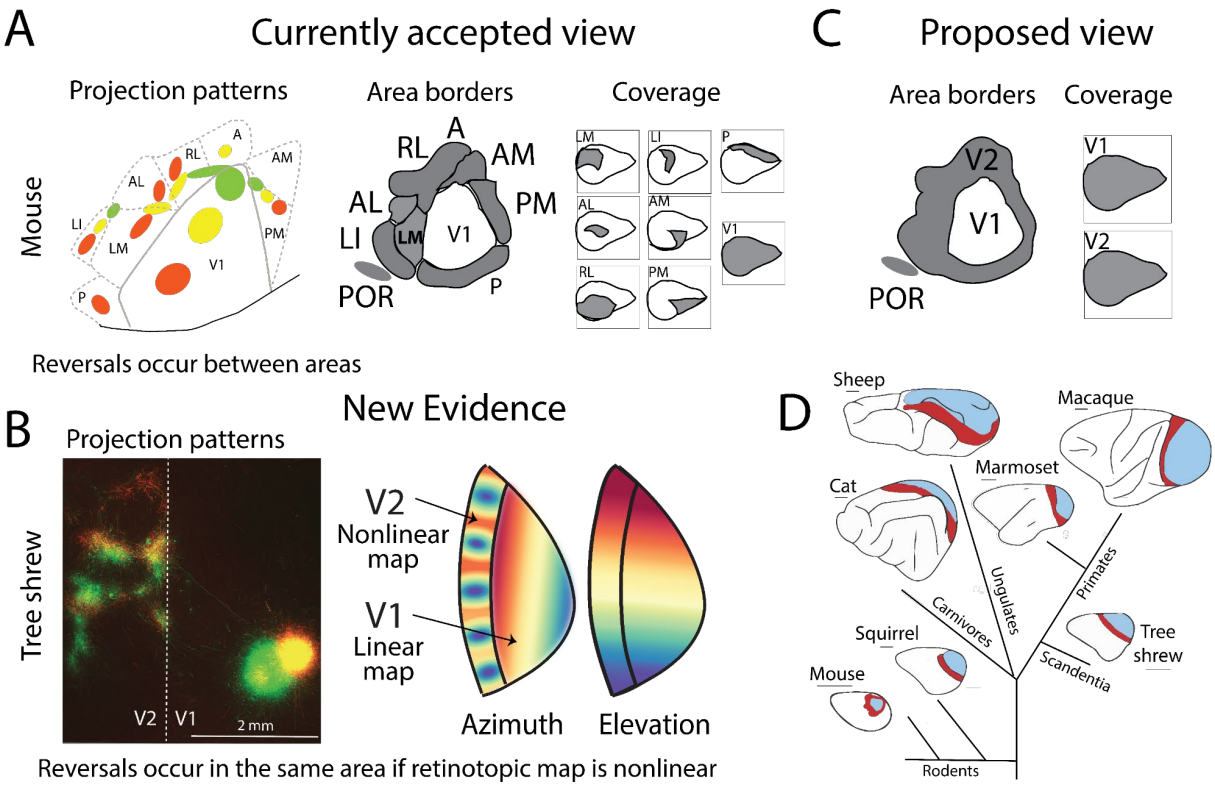

Figure 1: Higher order visual areas in the mouse may be better classified as a single area V2. A critical re-examination of functional and anatomical data supporting the current view of multiple higher order visual areas, each with partial and biased coverage of the visual field(A), coupled with new evidence of visual field reversals within single areas in the tree shrew (B), and marmoset (not shown) supports a new view (C) wherein a single area V2, with full coverage of the visual field, borders V1 in the mouse, similar to most other mammals.

Anatomical evidence for multiple higher order visual areas can be explained by nonlinear retinotopy in a single area V2

Efforts to understand the organization of the mouse visual system were largely based on prior anatomical and functional measurements in primates. Early parcellations of the mouse visual cortex were made based on cytoarchitectural features including cell density and laminar distribution - leading to the delineation of two subcomponents of a single area V2 (Caviness, 1975). Future work showed boundaries in labeling of histological markers such as SMI-32 and m2ChR labeling, but such changes mostly delineated area LM/AL (Wang et al., 2011) and seemed to be correlated with the representation of the lower visual field. We now know, based on work in both mice and primates that different parts of the retinotopic map of a single visual area can exhibit different genetic and molecular markers, different cell types, different cell density, and robustly different anterograde and retrograde connections to other areas (Morimoto et al., 2021; Mundinano et al., 2019; Palmer & Rosa, 2006; Yu et al., 2015). Therefore, observations of histological differences in higher order visual cortex, on their own, cannot be used to delineate areal boundaries.

Later parcellations of the mouse visual cortex relied, in addition to cytoarchitecture, on the pattern of anterograde connections from V1 to higher order visual cortex, as well as the pattern of callosal connections from contralateral V1 into ipsilateral higher order visual cortex. Combining these projection patterns revealed a complex set of modules in higher order visual cortex - each assumed to be a separate area. We now know that both the modular mirror-map organization of anterograde projections from V1, and callosal projections from contralateral V1, can be explained by non-retinotopic mapping within a single visual area. The definition of a single visual area despite the appearance of multiple mirror maps, or reversals, relies on the existence of a single mapping of a visual field - with a nonlinear transformation occurring between the retina and V2. This is precisely the case in the visual cortex of the mouse, where multiple modules (currently defined areas) combine to form a single, nonlinear, representation of the visual field. Each module, when considered alone, represents only a subsection of the visual field, with little overlap between modules (Fig 1A). Therefore, given what we now know about nonlinear retinotopic transforms, observations of patchy and modular projections from V1 cannot be used to delineate areal boundaries.

In addition to cytoarchitecture and connection patterns, a third anatomical feature used to delineate the primate visual cortical hierarchy is pairwise asymmetries in feedforward and feedback connection densities and laminar distributions. Specifically, feedforward inputs tend to terminate in primate layer 4 whereas feedback inputs tend to terminate in superficial and deep layers, but not in layer 4. In the rat and mouse, the laminar distribution is less distinct between feedforward and feedback inputs, but D'Souza et al. (2022) discovered a pattern specific to the mouse, focused on differences between Layer 1 and Layer 2-4. Feedforward inputs tend to terminate in Layers 2-4, but not in Layer 1, and feedback inputs tend to terminate in Layer 1, and less so in Layers 2-4. One can quantify this relationship using an optical density ratio (ODR) of labeling density in Layer 1, vs. all layers. An analysis based on such laminar differences easily distinguished V1 as providing feedforward input to higher order areas, with ODR values less than 0.5. Higher order areas were also easily distinguished as providing feedback inputs to V1, as evidenced by ODR values significantly greater than 0.5. However, the connections between higher order visual areas exhibited ODR values near 0.5, suggesting that these areas form neither feedforward nor feedback connections to each other, but are rather at the same level of the hierarchy. This lends further support to the unification of these higher order areas into a single V2, producing a simple 2-layer shallow hierarchy in the mouse visual cortex consisting of V1, V2, and perhaps the outlier area POR as a third layer.

Nonlinear retinotopy within a single visual area can recapitulate the appearance of multiple higher order areas in mouse visual cortex

Until improved tracing techniques allowed anatomical mapping of visual field representations beyond V1, the region of visual cortex immediately adjacent to V1 was originally designated as simply V2 based on its cytoarchitecture. The projection studies, however, showed several reversals in progression of the visual field, similar to those observed across the border of V1 and V2 in primates. These reversals were used to delineate area boundaries in the mouse, which produced a series of higher order areas with only partial coverage of the visual field. However, as discussed above, multiple visual field reversals can be a hallmark of nonlinear retinotopic mapping within a single area. We set out to explain the reversals beyond mouse V1 with an elastic net model of retinotopy in mouse higher visual cortex. To apply the modeling techniques used in previous papers we first needed to account for key differences in anatomy including the 'tear-drop' shaped visual field and the shape of the areas in the cortical sheet (Figure 2A). This included modifying the algorithm to weight the interactions between neighbors by the inverse square of their distance in cortical space to account for non-evenly spaced nodes.

Lower smoothness was also expected in the mouse. Despite having a similar retinal cone density as the peripheral retina of a primate, the mouse's smaller eyes result in low spatial resolution as the visual field is projected through the pupil onto a smaller retinal surface. In V1 this results in much larger receptive fields and beyond this, allows for bigger steps in the visual field to be taken by adjacent regions of cortex while preserving an overlapping representation. Given this, we expected that a lower smoothness constraint in our model may result in a better representation of the higher order visual areas' retinotopy (Figure 2B).

Here we show that nonlinear retinotopy within a single visual area can recapitulate the appearance of multiple areal borders: Self-organizing mechanisms explain nonlinear retinotopy producing visual field reversals in mouse visual cortex. Figure 2 shows the outcome of an example instance of the model. A single area following the shape of mouse higher order visual areas trained to cover the mouse visual field often (but not always) creates retinotopy with reversals that align to those reported in the mouse. This implies such nonlinear mapping is optimal when constraints of the mouse visual cortex are accounted for.

The precise layout of these reversals varies somewhat with the initial random seed, but always includes multiple reversals in the upper and lower visual field representations. We note that variation also exists in the reported retinotopy of the mouse between animals (Garrett et al., 2014; Zhuang et al., 2017). There may also be additional constraints in the mouse visual cortex that are not accounted for in our model that could result in a more robust outcome. Further work is needed to create a more reliable model, but the model as it stands demonstrates the feasibility of a single mouse V2 to account for the nonlinear retinotopic mapping, multiple visual field reversals, and the appearance of multiple visual areas under the false assumption of linear retinotopy.

This undermines the original motive for the parcellation of the region of cortex into multiple areas and suggests that reverting to the original hypothesis of a single area, in line with other animals, may be a more parsimonious explanation of mouse visual cortex. However, multiple differences between these areas along anatomical and functional lines have also been reported. Next, we will review and assess if a single V2 area with a warped retinotopy could account for these differences.

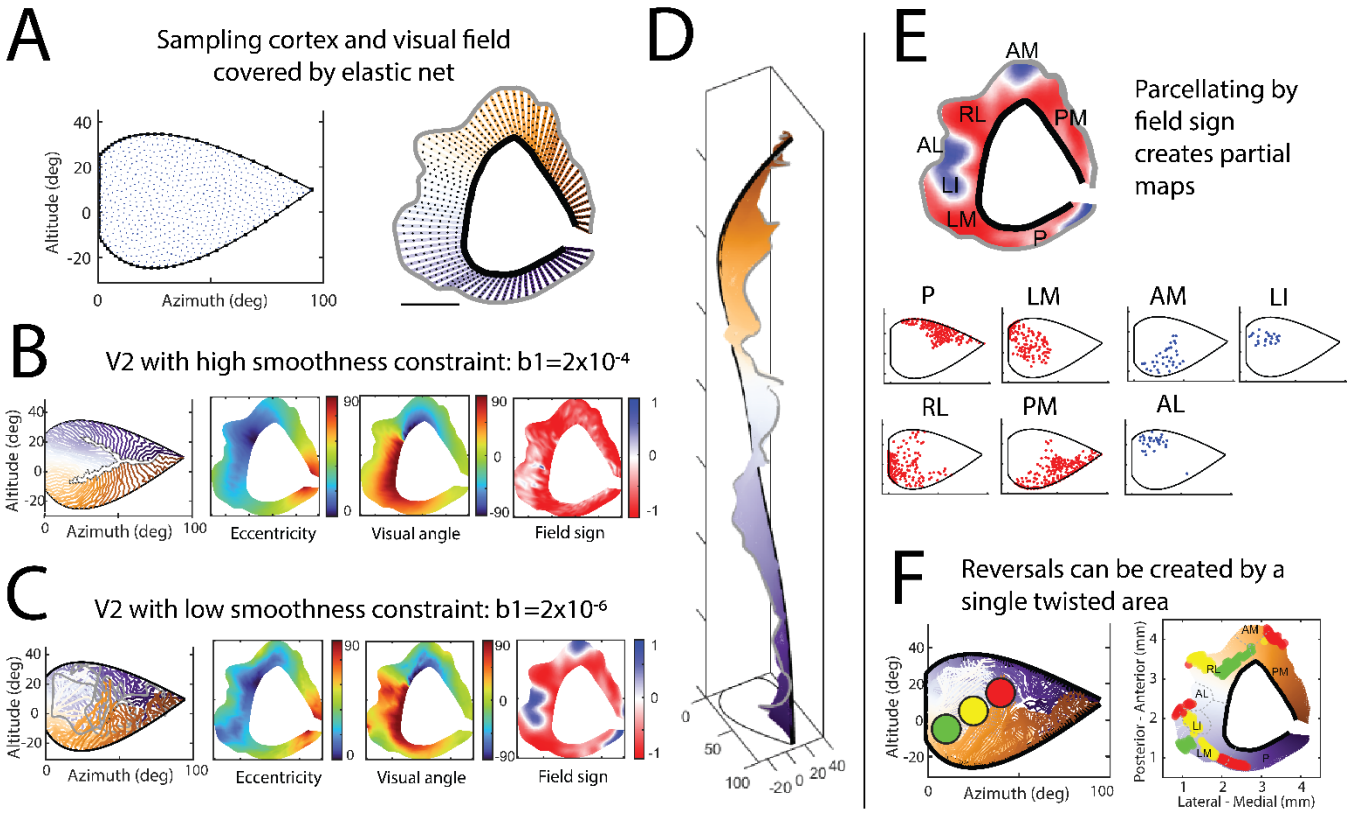

Figure 2: Retinotopic models show emergence of a single nonlinear map of visual space beyond mouse V1. We extended the elastic net model from previous work to constrain a model of V2 to the unique structure of the mouse. A) Borders of cortical space were traced from Zhuang et al. and a teardrop shaped visual field was used to approximate the full visual field covered by mouse V1. B-C) As in the previous work, modifying the constraints to smoothness and isotropy result in internal reversals, seen in alternating field sign (Sereno et al., 1994). D) Visualization of the visual field, x & y plane, covered by normal lines between the V1 and higher order visual area border as in right of A. These lines are stacked on the Z-axis, and color code, going from the caudal border of V1 in purple around the circumference of V1 to the medial edge in orange. The V1 border, black line, anchors the retinotopy to the outer edge of the teardrop shaped visual field. The outer border, gray line, is free to find the point in visual space to optimize coverage under constraints. Like a ribbon pulled taut, in the case of high smoothness, ie B, this edge stays near the center of the visual field while the V1 edge rotates around it. In the case of low smoothness in C & D, the 'ribbon' is more elastic and the free edge swings back and forth over the center of the visual field. Note that the distance between adjacent nodes increases along the lines from the inner to outer border, loosening the weights on the smoothing constraint as it expands into the cortical surface. E) This nonlinear retinotopy generates, from a single continuous area, reversals that approximately match mouse higher order visual areas, showing that previously reported retinotopic maps in mouse higher order visual areas are parsimonious with a single area covering a full, but twisted, visual field. F) Matching points in the visual field with their locations in this single area, creates similar patterns to what has been shown in tracer studies, compare 1A.

Reported functional property differences among higher order areas are better explained by retinotopy through eccentricity and opsin gradients

Unlike in the primate visual cortex, where individual areas are marked by their distinct functional difference, in the mouse functional property differences across areas are distributed topographically and continuously, and consistent with the ethological relevance of visual field locations. Therefore, a more parsimonious explanation may be provided by retinotopy-based differences within a single area V2 rather than different areas. To assess this, we reanalyzed a dataset from Han et al. (Han et al., 2022) and showed that some of the reported differences in SF and TF tuning can be accounted for by a smooth function of eccentricity and altitude. The relationship of tuning with eccentricity is unexpectedly inverted from what has been reported in V1, but is nonetheless still smooth. Some relationship between tuning properties and eccentricity, within single areas, is common in other animals and should be expected here.

In primate vision research ‘eccentricity’ is used to mean distance in visual degrees from the center of gaze, which is a useful metric for animals with a fovea and robust overrepresentation of the central few degrees of vision. Many tuning parameters scale with eccentricity within visual areas, making it a very important parameter to control for in foveal animals such as primates. However, in the afoveate mouse, ‘center of gaze’ is difficult to control for and typically altitude above eye level and azimuth relative to a normal through the eye are used.

While this is a reasonable approach for an animal without a fovea, it has been reported that there is a central region of the upper binocular visual field that is overrepresented in V1, and seems to be behaviorally significant: the ‘focea’ (van Beest et al., 2021). Due to strong expectations from animals that tuning may scale with distance from this point, we will assess whether tuning varies with distance from this point (20 degrees above resting eye level on the vertical meridian) referred to in figure 3 as ‘eccentricity from fovea’ in degrees of visual field.

There is an additional effect across retinotopy in the mouse that also needs to be taken into account. The mouse retina has a gradient of cone opsins such that S-cones, sensitive to UV light, are overrepresented on the ventral surface (the upper visual field) and give way to M-cones, sensitive to green light, on the dorsal surface (the lower visual field). When a typical LCD monitor is used, M-cones but not S-cones, are partially activated (Rhim et al., 2021). This means that retina in the upper and lower visual fields are in a rod-dominated scotopic and mixed cone- and rod- mediated mesopic regime respectively. This retinal gradient is known to be preserved in the visual cortex (Rhim et al., 2017) and is thought to play an important role in predator evasion (Qiu et al., 2021). Thus, control for the opsin gradient is crucial for accurate measurement, reporting, and comparative analysis of functional properties in mice. Specifically, the use of typical LCD monitors results in primacy of scotopic vision in the ventral retina, producing higher spatial and lower temporal frequency tuning in the upper visual field.

In Han et al. (2022) an LCD screen was used, and a tendency towards higher SF tuning in the areas with predominantly upper field representations suggests that the cone opsin gradient may be a factor. To account for the effects of both eccentricity from the fovea and the cone opsin gradient we fit a plane to these tuning parameters as a function of these variables, based on crude estimates of center of mass of retinotopic location of each area. The fitting for SF and TF was done on all cells that were bandpass tuned within the range of stimuli presented, excluding cells that had reported tuning to the extreme edges of the range. We also excluded area P as this area wasn’t separated from POR in this study. Subtracting the expected value for tuning of each cell due to the linear effects of eccentricity and altitude, the differences between areas in the residuals are greatly diminished.

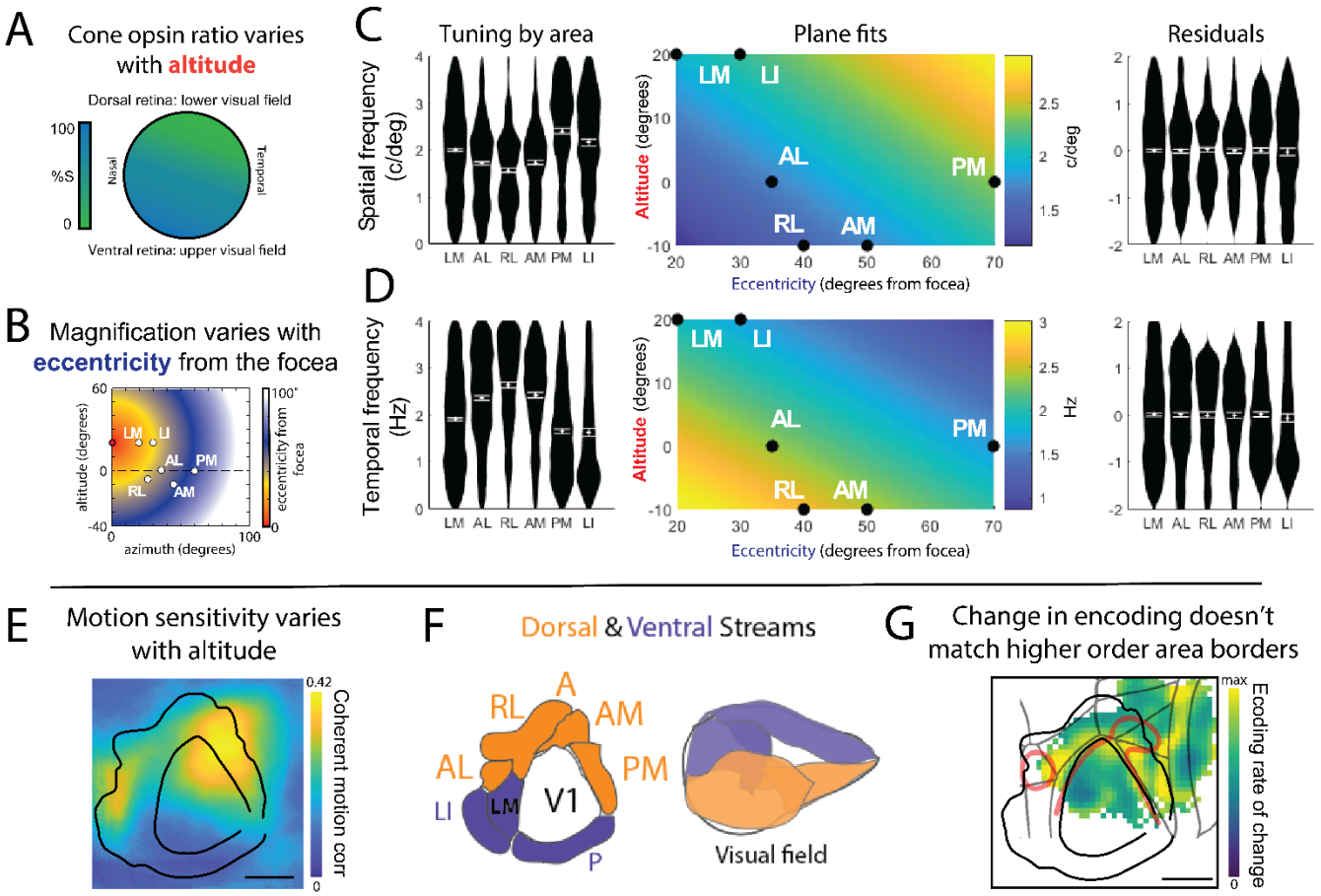

Figure 3: Retinotopy accounts for functional variations between higher order visual areas. A) Schematic of retinal cone opsin gradient following (Demb and Singer, 2015) B) Schematic of eccentricity from fovea with area estimates for the data used in C&D. C) Data from (Han et al. 2022). Tuning to spatial frequency of bandpass cells in each area (left), plane fit of SF to area altitude and eccentricity from focea (middle) and the residuals (right) after subtracting a plane fit. D) Same for temporal frequency. Area tuning violin plots show the distribution of tuning within areas with white dots for the mean and lines for 95% confidence interval. Ttest corrected for multiple comparisons for SF and TF show no significant pairwise differences between the means of the residuals (although distributions remain significantly different, possibly due to internal retinotopy). E) Map of motion sensitivity adapted from Sit & Goard (2020) showing higher sensitivity in the lower field representation of V1 and higher order visual areas. F) Dorsal and Ventral streams in the mouse containing multiple of the higher order visual areas have been suggested due to differences in function, however these map closely onto vertical retinotopy. G) Behavioral encoding as a function of cortical space shows large change along the V1 border, but not between higher order visual areas (Minderer et al. 2020). Scale bar 1mm

Spatial frequency varying smoothly with eccentricity within an area is similar to what is seen in other animals. However, in this case the relationship seems to be inverted: tuning to higher spatial frequencies is seen in the periphery compared to central vision. This has been reported in higher order visual areas consistently (Marshel et al. 2011, Han et al. 2022). This doesn't affect our reinterpretation of the areal designations, but this unexpected observation is made even more obvious when this region of cortex is considered as a single area.

Functional feature differences are one of the metrics used to justify areal definitions in the higher order visual system of primates and cats. For instance, area MT in primates exhibits sensitivity to global motion direction that is absent in area V2, even in identical regions of the visual field. Such hierarchical and parallel processing of overlapping parts of the visual field is thought to represent an efficient strategy to build selectivity to complex input

features. While there is growing evidence of functional diversity within mouse visual cortex, most observations of diverse functional properties report smooth continuous changes in tuning across multiple areas, rather than robust differences between higher order areas. For instance, binocular disparity tuning (Chioma et al., 2019), color tuning (Aihara et al., 2017), and coherent motion processing (Sit & Goard, 2020) have all recently been shown to vary across the elevation axis of retinotopy. Similarly, receptive field size, response latency, and the degree of phase-locking to drifting gratings vary smoothly across higher order visual areas, along the azimuth axis of retinotopy (Siegle et al., 2021). Finally, encoding of behavioral task-related features has shown to vary across higher order visual areas of the mouse (Minderer et al., 2019), but as the authors point out, this variation is agnostic to higher order areal boundaries and instead follows the underlying topography smoothly (Figure 3G). In fact, the only functional discontinuities in the mouse posterior cortex were found at the major anatomical borders between V1, parietal, and retrosplenial areas.

Based on this data, we believe the functional feature differences observed across the mouse higher order visual system can be explained more parsimoniously by variations in retinotopy rather than areal identity. This limits the use of functional feature diversity in justifying areal definitions. In order to rely on functional feature differences to assess areal identity, the confound of retinotopy must be removed. This is typically done by reporting functional feature differences across areas, in overlapping parts of the visual field representation of each area. The studies mentioned above do not carry out this important control, largely due to the fact the higher order visual areas in the mouse do not have overlapping representations of the visual field (Zhuang et al. 2017). This lack of visual field overlap across areas, is in itself, suggestive of a lack of hierarchical multi-area processing in the mouse. The lack of visual field overlap combined with the observed smooth changes in functional feature tuning strongly supports the re-classification of multiple higher order visual areas into a single area V2. Such an area would exhibit the observed functional feature differences in different parts of its visual field map, as has been observed in primates and cats. Such differences ultimately arise due to the presence of different types of ethologically relevant information in distinct parts of the visual field (Sedigh-Sarvestani et al. 2022).

Discussion:

Here we have made a case, using simulations and a critical analysis of published literature, that many of the higher order visual areas in the mouse are actually sub-parts of a single area V2. We have shown that multiple visual field reversals, on their own, cannot be used to delineate areal boundaries. We have also shown that many of the functional property differences reported between higher order areas are better explained by known differences in functional feature preference across the retinotopic map of a single visual area. However, there remains some evidence against the hypothesis of a single V2 in mouse visual cortex. Harris et al. (Harris et al., 2019) used the laminar density of projection patterns between different cortical and subcortical regions to give classification scores to the different higher order visual areas and have found significant different hierarchy scores for these areas. However, they note that the hierarchy they found was much shallower than expected, particularly between these areas, and it's unclear whether hierarchical scores at different retinotopy regions of a single area might generate similar results. More work will need to be done to definitively determine whether this hypothesis is correct.

Recent advances in our understanding of nonlinear retinotopy and a re-evaluation of published data strongly supports redefining mouse higher order visual areas into a single area V2. What remains, is a visual system with distinct properties across its visual field - aligned with ethological needs and behaviors. This new definition produces a common set of rules for defining areal boundaries among mammals: the presence of a full visual field, homogenous cytoarchitecture and smooth functional properties, and would bring mice into agreement with evolutionary evidence for a single area V2 in other nearby lineages (Rosa and Krubitzer, 1999).

We note, again, that our argument is not novel. Rosa and Krubitzer made the same argument and plea in 1999, based on the presence of a single area V2 in a large range of mammals and other non-mouse rodents (figure

1D). We build on their argument armed with the knowledge of nonlinear retinotopy that can explain the apparent differences in anatomy and function. More importantly, we believe the distinction of a single area into multiple areas has misled the field in both experimental design and interpretation of data collected from mouse visual cortex. Therefore, a redefinition is not merely a matter of semantics but rather necessary for improved studies of the visual system.

We believe in the value and urgent need for cross-species comparisons in neuroscience. This manuscript presents an effort on our part to align the mouse with other mammals. With a single area V2 definition, the mouse visual cortex is no longer an outlier in the evolutionary tree. This means we can continue to rely on this species to gain knowledge about the mammalian visual system. Otherwise, we should think carefully about whether what we learn in the mouse can be applied to any other mammal.

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