Reviewer's report

Title: Multivariate Profiling of Neurodegeneration-associated changes in a Subcellular Compartment of Neurons via Image Processing

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Reviewer: ralph a. Nixon

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"Multivariate Profiling of Neurodegeneration-associated Changes in a Subcellular Compartment of Neurons Via Image Processing"

The authors of this manuscript outline a new method to provide a high-throughput screening of a specific pathological manifestation related to Alzheimer’s disease- morphological changes in the endolysosome. They use a well-developed model of endolysosomal dysfunction, the blue cheese mutant of Drosophila. The authors further validate their method by challenging their trained SVM to predict the genotype of an image of unknown origin with a high success rate. There is value in their study in that there is a level of discrimination using Fisher’s linear discriminant, despite the subtlety of differences between experimental conditions.

Discretionary Revisions

There are shortcomings in current segmentation and edge detection methods. In order to support the value of their screening, the authors could have done a side-by-side comparison of their method either to some other mode of measurement routinely used today or, perhaps, simply by performing their assay on unfiltered images and highlighting those differences. They refer to their screening as rapid and unbiased, yet do not substantiate this claim by many measures. Detected endolysosomal spots from their filtered image should be made apparent in red in Figure 4B (as stated in the legend), yet there is no color present in that figure.

Furthermore, the authors use a very specific, fairly clean system (in terms of lysosomal models) for developing and validating their technique. The value could have been reinforced by outlining it in their Drosophila system, then testing it in another experimental paradigm or cell culture model.

Overall, it is valuable to have a method for performing unbiased multivariate profiling of endosomes, but more evidence that the outlined methods excels over what is currently available, in side-to-side comparisons, would have strengthened the presentation.

Level of interest: An article of importance in its field

Quality of written English: Acceptable
**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.