A comparison of retinal nerve fiber layer thickness in pseudopapilledema and papilledema

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Executive Summary

Introduction

In clinical practice, a common dilemma is to distinguish pseudopapilledema from pathologic optic disc edema. Diagnosis and management of pseudopapilledema and papilledema are vastly different. However, frequently, patients with elevated optic discs are almost always referred for neuro-ophthalmologic evaluation and may be subjected to neuroimaging, lumbar puncture, and other laboratory studies. It is more challenging to the practitioner when patients have papilledema superimposed on pseudopapilledema because patients with pseudopapilledema have elevated optic nerve head appearances at baseline. It is important to note that papilledema is a serious clinical sign that may represent underlying threatening intracranial pathology. Similarly, it is as important to recognize features of pseudopapilledema to avoid unnecessary costly and invasive tests.

Optical coherence tomography (OCT), a non-invasive imaging method, which creates in vivo cross sections of the retina, has been a valuable tool and is used to understand some neurological diseases such as optic neuritis, multiple sclerosis, spinocerebellar ataxia, neuromyelitis optica, pituitary tumors and Parkinson's disease. Studies have compared retinal nerve fiber layer (RNFL) thickness in patients with pseudopapilledema and papilledema.
The purpose of this study is to evaluate and characterize findings of patients with pseudopapilledema and papilledema superimposed pseudopapilledema to help clinicians understand disease progression and resolution by describing patients with papilledema superimposed on pseudopapilledema, assessing the upper-limit of RNFL thickness in patients with pseudopapilledema, identifying differences in variability of RNFL measurements of patients during follow-up, and proposing recommendations on how to approach patients with pseudopapilledema.

Data was collected from 2010-2017, a 6-year period, from the database of patients of the neuro-ophthalmology service at New England Eye Center at Tufts Medical Center, Boston Massachusetts Twenty-four eyes of 12 patients were included in pseudopapilledema group and 14 eyes of 7 patients were included in papilledema superimposed on pseudopapilledema group. Statistical analysis and machine learning techniques were used to evaluate the the accuracy of predicting whether a patient has pseudopapilledema or the more serious papilledema. Such a predictive model could potentially aid in diagnosis resulting in cost savings and increased patient safety by reducing the need for invasive tests.

##**Results**

Data Cleaning

Let's check the structure of the data.

```
## 'data.frame':    2546 obs. of  12 variables:
##  $ IID                  : int  1 1 1 1 1 1 1 1 1 1 ...
##  $ group                : int  1 1 1 1 1 1 1 1 1 1 ...
##  $ gender               : int  1 1 1 1 1 1 1 1 1 1 ...
##  $ age.at.presentation  : int  10 10 10 10 10 10 10 10 10 10 ...
##  $ duration.of.follow.up: int  51 51 51 51 51 51 51 51 51 51 ...
##  $ time                 : int  0 1 2 3 4 5 6 7 8 9 ...
##  $ average.RNFL         : int  185 162 169 190 NA NA NA NA 162 NA ...
##  $ RNFL.I               : int  222 218 216 261 NA NA NA NA 238 NA ...
##  $ RNFL.S               : int  226 202 210 262 NA NA NA NA 193 NA ...
##  $ RNFL.N               : int  223 135 172 157 NA NA NA NA 141 NA ...
##  $ RNFL.T               : int  68 92 78 78 NA NA NA NA 75 NA ...
##  $ eye                  : int  1 1 1 1 1 1 1 1 1 1 ...
```

```
##       IID             group           gender      age.at.presentation
##  Min.   : 1.00   Min.   :1.000   Min.   :1.000   Min.   :10
##  1st Qu.:14.00   1st Qu.:1.000   1st Qu.:1.000   1st Qu.:17
##  Median :27.00   Median :1.000   Median :2.000   Median :33
##  Mean   :26.84   Mean   :1.368   Mean   :1.684   Mean   :31
##  3rd Qu.:46.00   3rd Qu.:2.000   3rd Qu.:2.000   3rd Qu.:41
```

```
##  Max.   :53.00   Max.   :2.000   Max.   :2.000   Max.   :59
##
##  duration.of.follow.up      time     average.RNFL       RNFL.I
##  Min.   : 6.00         Min.   : 0   Min.   : 71.0   Min.   : 57.0
##  1st Qu.:11.00         1st Qu.:16   1st Qu.:100.8   1st Qu.:138.0
##  Median :30.00         Median :33   Median :126.5   Median :168.0
##  Mean   :29.58         Mean   :33   Mean   :140.8   Mean   :195.4
##  3rd Qu.:45.00         3rd Qu.:50   3rd Qu.:165.5   3rd Qu.:229.8
##  Max.   :66.00         Max.   :66   Max.   :469.0   Max.   :628.0
##                                     NA's   :2378    NA's   :2380
##      RNFL.S           RNFL.N          RNFL.T           eye
##  Min.   :  67.0   Min.   : 14.0   Min.   : 42.00   Min.   :1.0
##  1st Qu.: 126.0   1st Qu.: 64.0   1st Qu.: 64.75   1st Qu.:1.0
##  Median : 163.5   Median : 83.0   Median : 79.50   Median :1.5
##  Mean   : 197.9   Mean   :102.9   Mean   : 87.03   Mean   :1.5
##  3rd Qu.: 222.0   3rd Qu.:120.0   3rd Qu.:101.25   3rd Qu.:2.0
##  Max.   :2811.0   Max.   :422.0   Max.   :313.00   Max.   :2.0
##  NA's   :2380     NA's   :2382    NA's   :2382
```

Features that should be factors are changed. Group, which indicates pseudopapilledema or papilledema, gender, and eye, which indicates left or right, should all be factors.

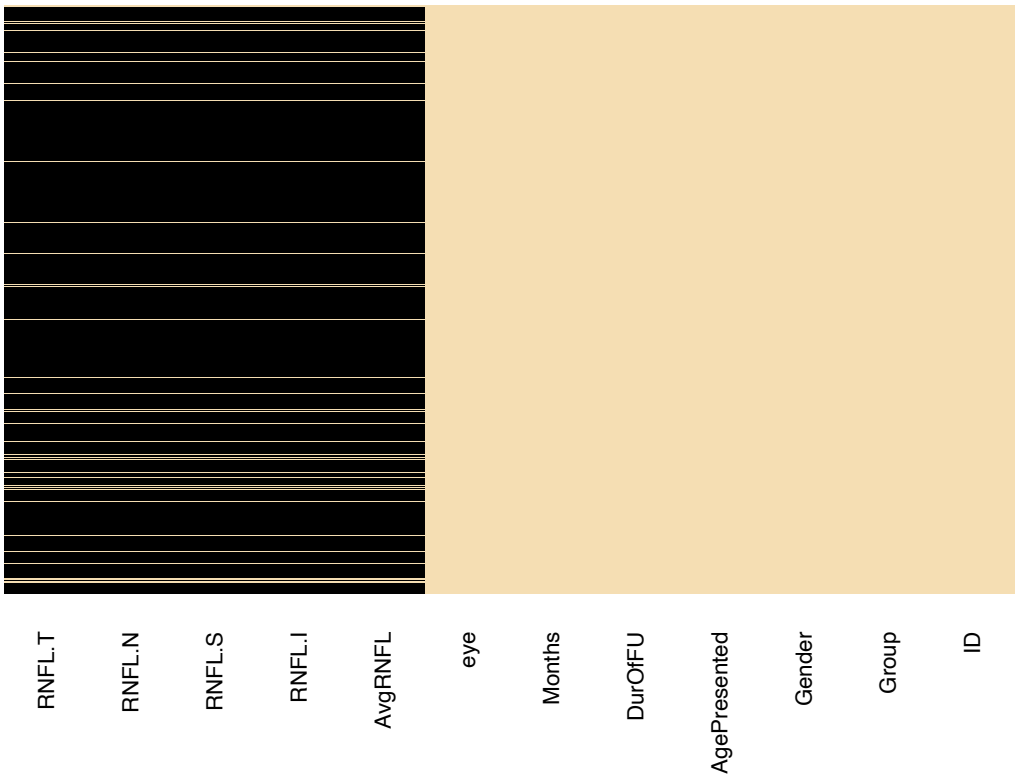
The column names are changed to make then more meaningful.

Gender is indicated as 2 for male and 1 for female. Group 2 indicates Papilledema and Group 1 indicates Pseudopapilledema, and eye 1 indicates the left eye, while 2 indicates the right eye. The values for these features will be changed to make them more meaningful. Several small functions are written to accomplish this.

Data Exploration

Missing Values

Let's check for missing values. The visits of each patient are recorded by month after the initial visit which is indicated as month 0. Every subsequent month, from 1 to 66, has a placeholder and this accounts for the multiple missing values.

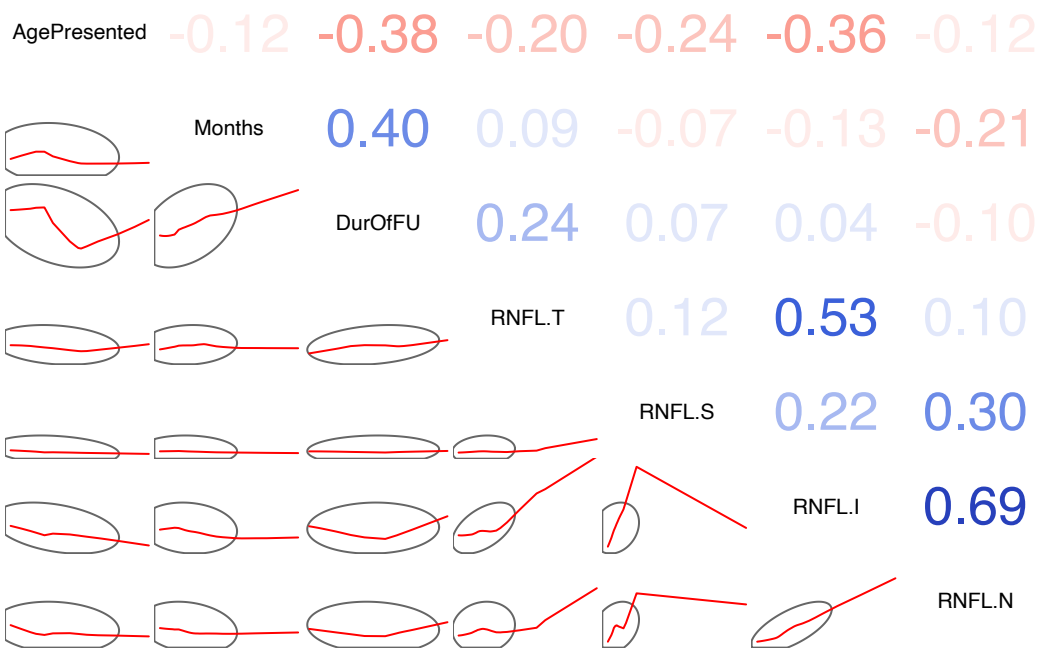


As these months in which a patient has no visits are not necessary we can remove them. There are no missing values for the patient demographic data.

After all missing values were removed the missing map chart shows no missing values.

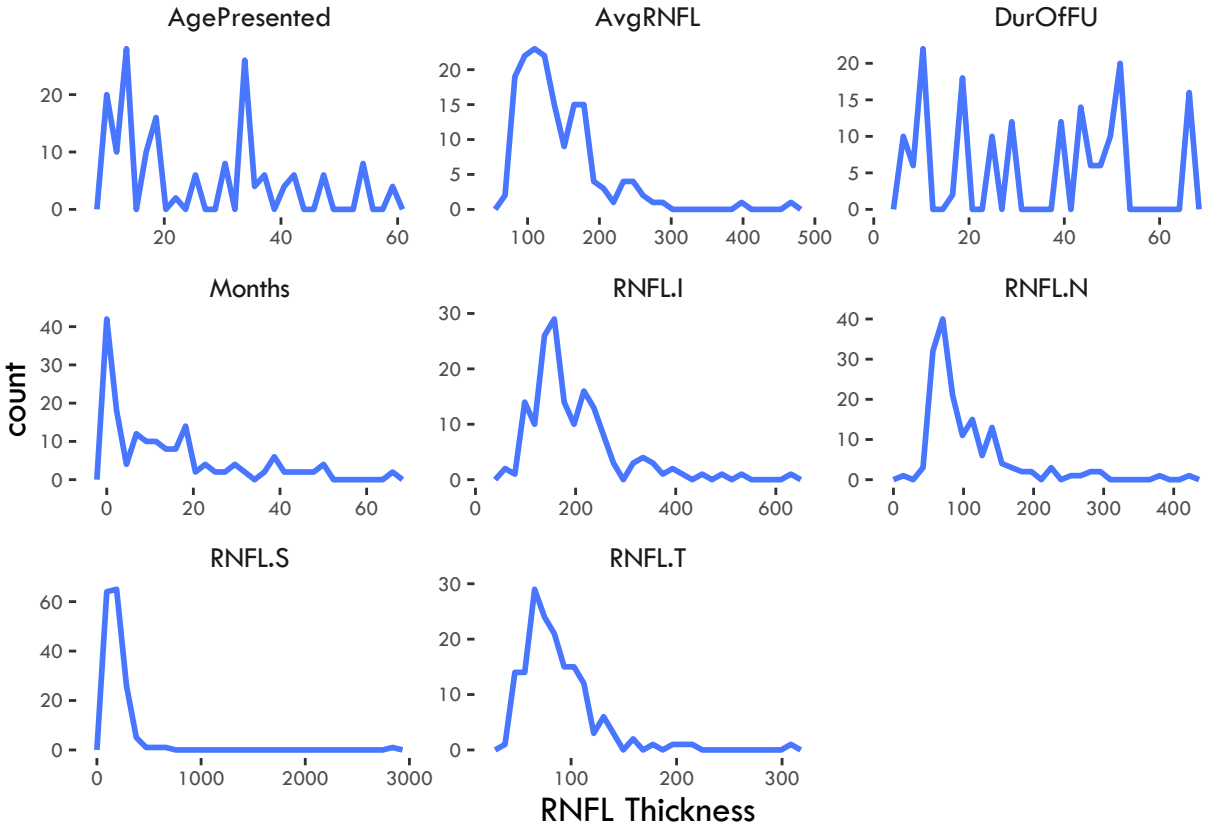
####**Correlations**

The average RNFL is not included here as it's a derived field that will be highly correlated with the other RNFL measures. Each RNFL measure is moderately correlated to each other in the left eye, but more strongly correlated in the right eye. RNFL.S is particularly strongly correlated with RNFL.I in the right eye ($r^2 = 0.8$). In the bottom panels long, narrow ellipses represent high correlations while circular ellipses represent low correlations.



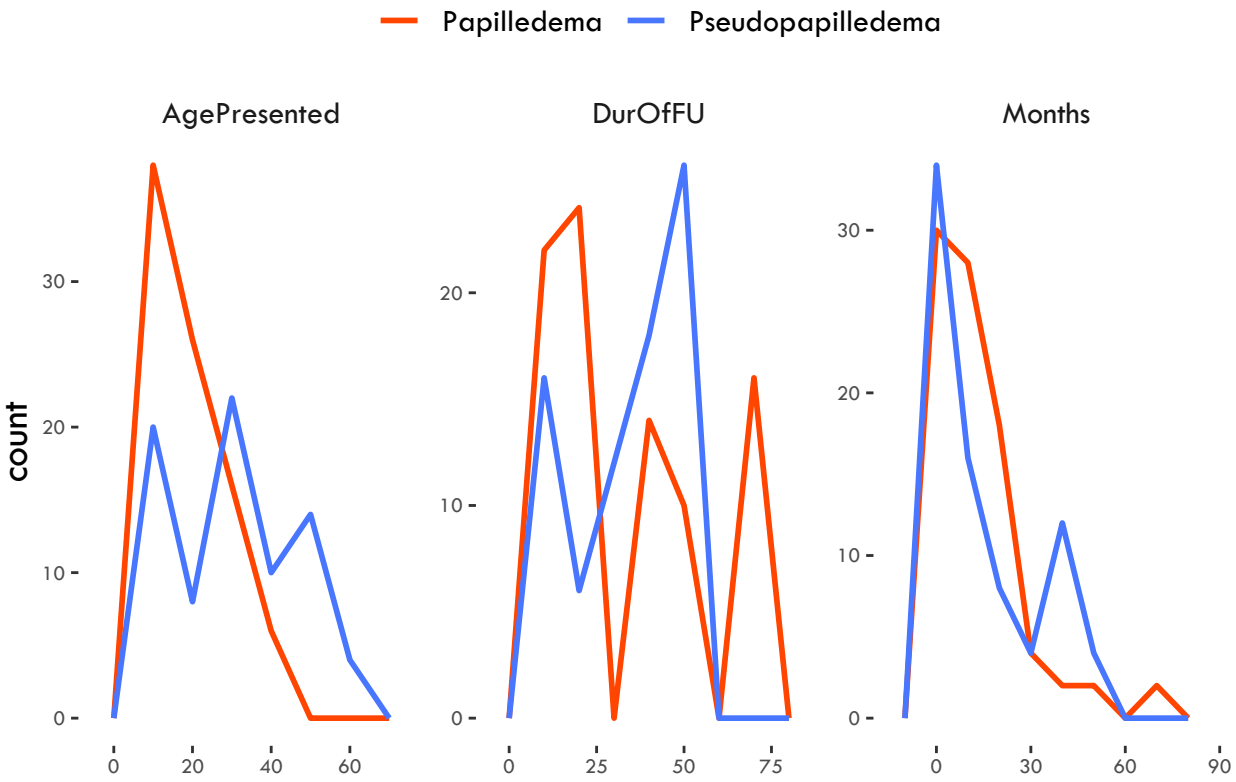
Distributions

The distributions of the numeric fields were examined. There are a wide range of ages, months, and visit durations. The continuous variables of interest show fairly normal unimodal distributions that are skewed to the right.

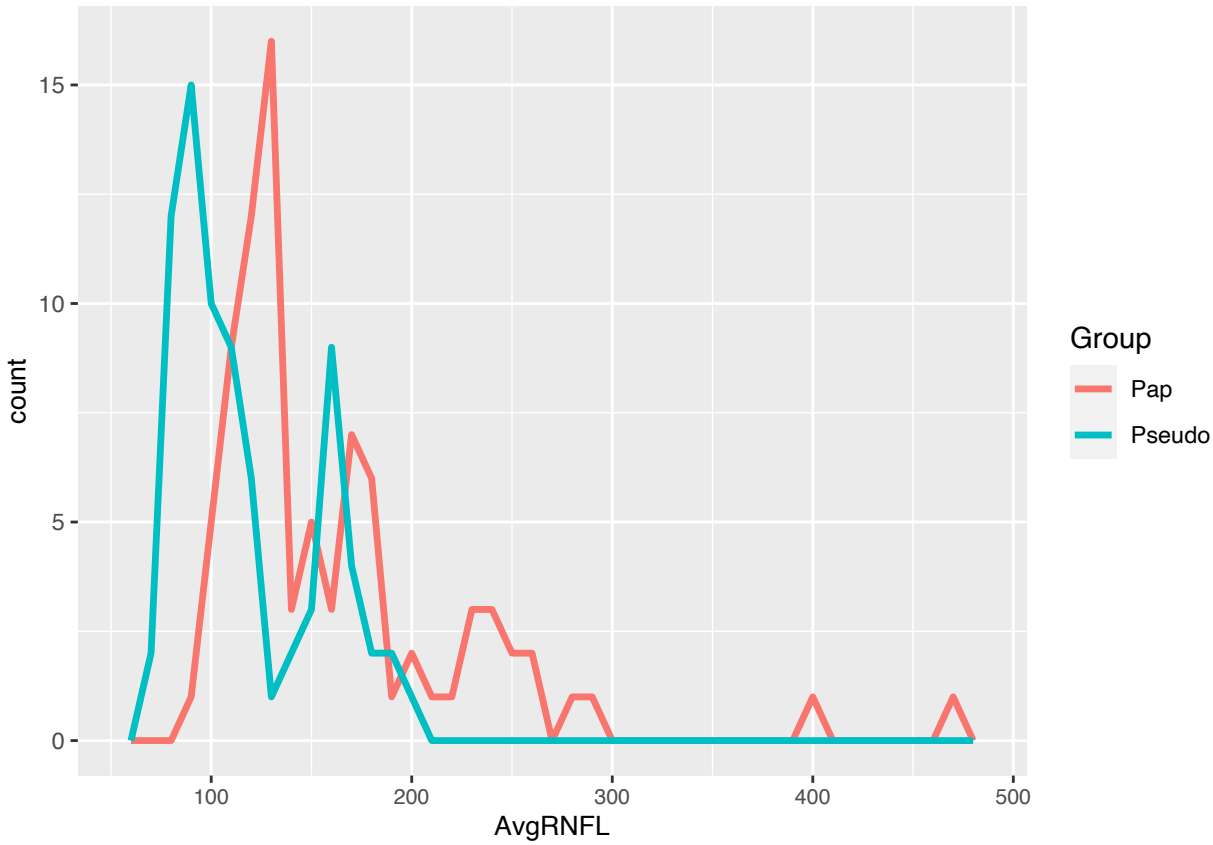


An examination of the distributions of Age, Duration and Month of Visit between Papilledema and Pseudopapilledema patients was made. The ages of Pseudopapilledema patients are more widely distributed. The

Papilledema patients are all below 40.The visit duration and months values are similarly distributed however Papilledema patients are more skewed to the higher values for these measures.



Next we examine the distribution of Average RNFL values between Papilledema and Pseudopapilledema patients. The average RNFL measurements from Papilledema patients are more highly skewed. Only Papilledema patients present average RNFL measurement over 200 μm.




```
## List of 1
##  $ text:List of 11
##   ..$ family       : chr "Tw Cen MT"
##   ..$ face         : NULL
##   ..$ colour       : NULL
##   ..$ size         : num 15
##   ..$ hjust        : NULL
##   ..$ vjust        : NULL
##   ..$ angle        : NULL
##   ..$ lineheight   : NULL
##   ..$ margin       : NULL
##   ..$ debug        : NULL
##   ..$ inherit.blank: logi FALSE
##   ..- attr(*, "class")= chr [1:2] "element_text" "element"
##  - attr(*, "class")= chr [1:2] "theme" "gg"
##  - attr(*, "complete")= logi FALSE
##  - attr(*, "validate")= logi TRUE
```

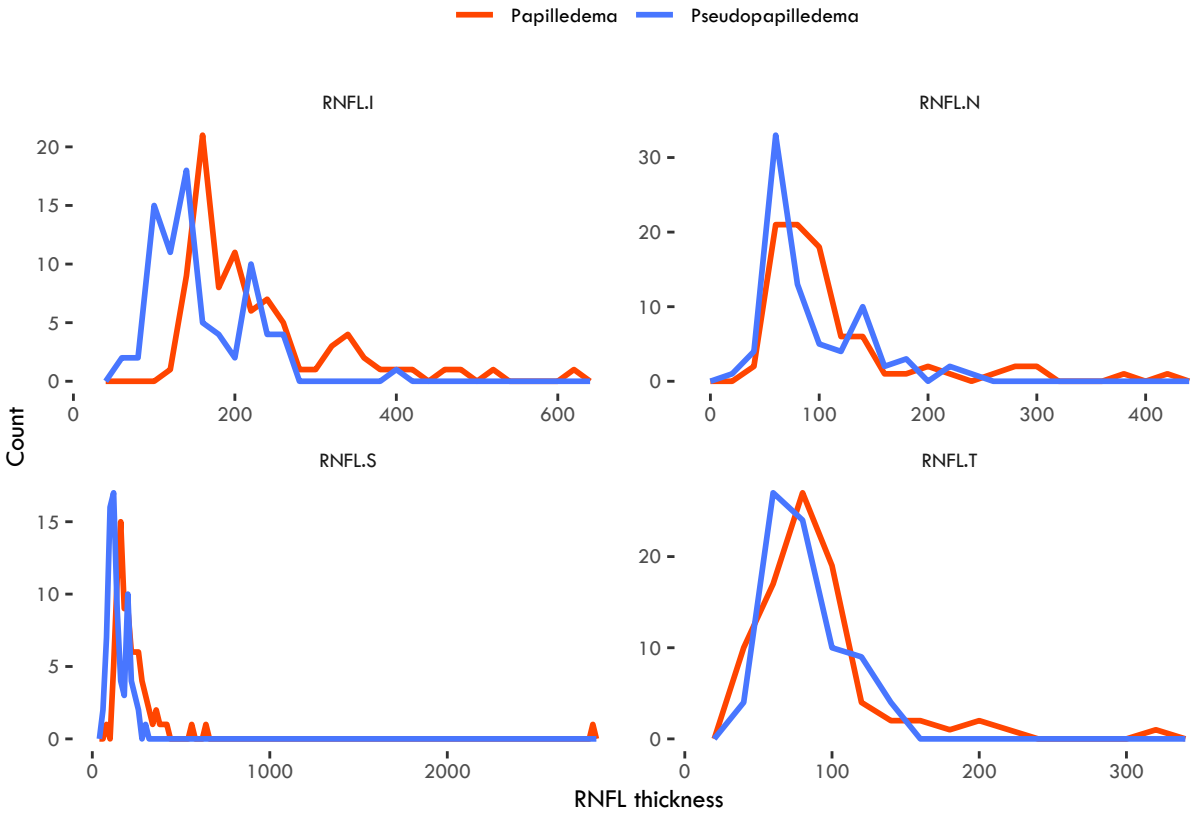
```
## List of 2
##  $ axis.text.y :List of 11
##   ..$ family       : NULL
##   ..$ face         : num 1
##   ..$ colour       : NULL
##   ..$ size         : num 8
##   ..$ hjust        : NULL
##   ..$ vjust        : NULL
##   ..$ angle        : NULL
```

```
##   ..$ lineheight   : NULL
##   ..$ margin       : NULL
##   ..$ debug        : NULL
##   ..$ inherit.blank: logi FALSE
##   ..- attr(*, "class")= chr [1:2] "element_text" "element"
##  $ legend.title: list()
##   ..- attr(*, "class")= chr [1:2] "element_blank" "element"
##  - attr(*, "class")= chr [1:2] "theme" "gg"
##  - attr(*, "complete")= logi FALSE
##  - attr(*, "validate")= logi TRUE
```

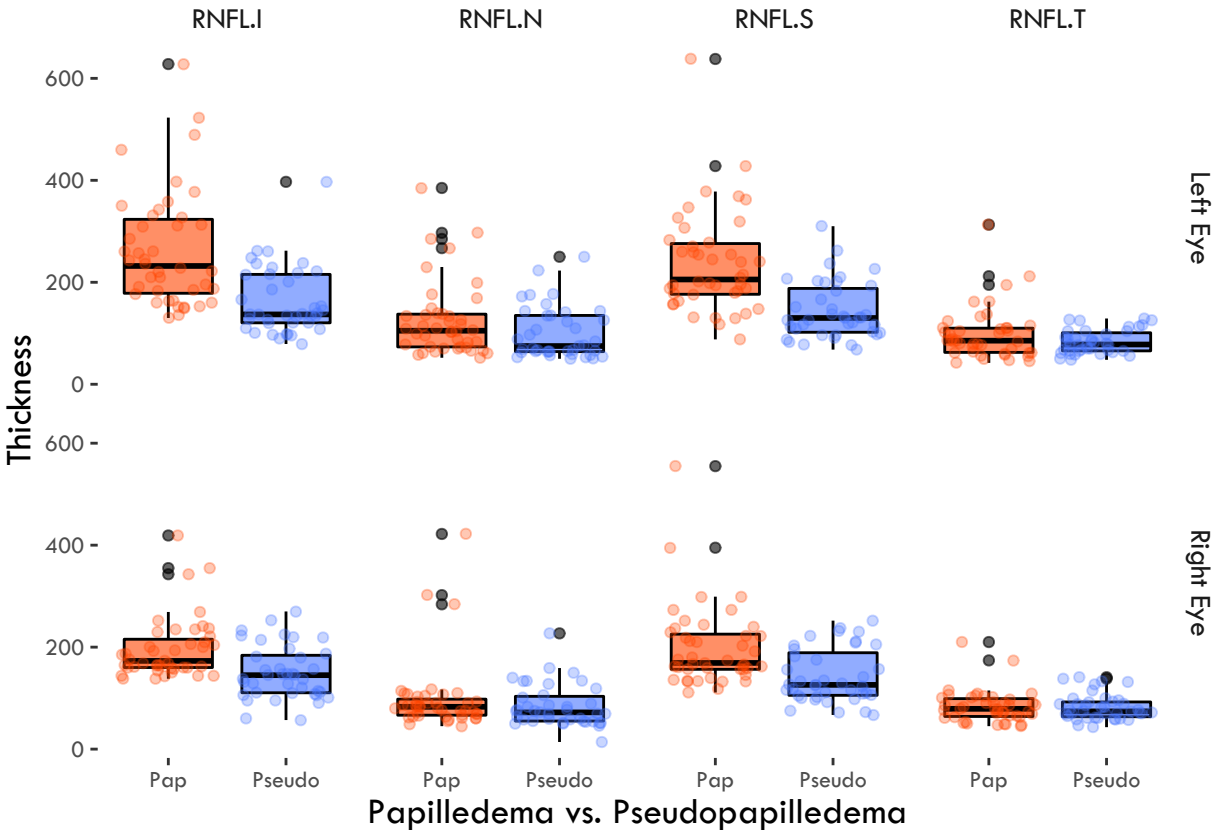
```
## <ggproto object: Class ScaleDiscrete, Scale, gg>
##     aesthetics: colour
##     axis_order: function
##     break_info: function
##     break_positions: function
##     breaks: waiver
##     call: call
##     clone: function
##     dimension: function
##     drop: TRUE
##     expand: waiver
##     get_breaks: function
##     get_breaks_minor: function
##     get_labels: function
##     get_limits: function
##     guide: legend
##     is_discrete: function
##     is_empty: function
##     labels: Papilledema Pseudopapilledema
##     limits: NULL
##     make_sec_title: function
##     make_title: function
##     map: function
##     map_df: function
##     n.breaks.cache: NULL
##     na.translate: TRUE
##     na.value: NA
##     name: waiver
##     palette: function
##     palette.cache: NULL
##     position: left
##     range: <ggproto object: Class RangeDiscrete, Range, gg>
##         range: NULL
##         reset: function
##         train: function
##         super:  <ggproto object: Class RangeDiscrete, Range, gg>
##     rescale: function
##     reset: function
##     scale_name: manual
##     train: function
##     train_df: function
##     transform: function
##     transform_df: function
```

```
##     super:  <ggproto object: Class ScaleDiscrete, Scale, gg>
```

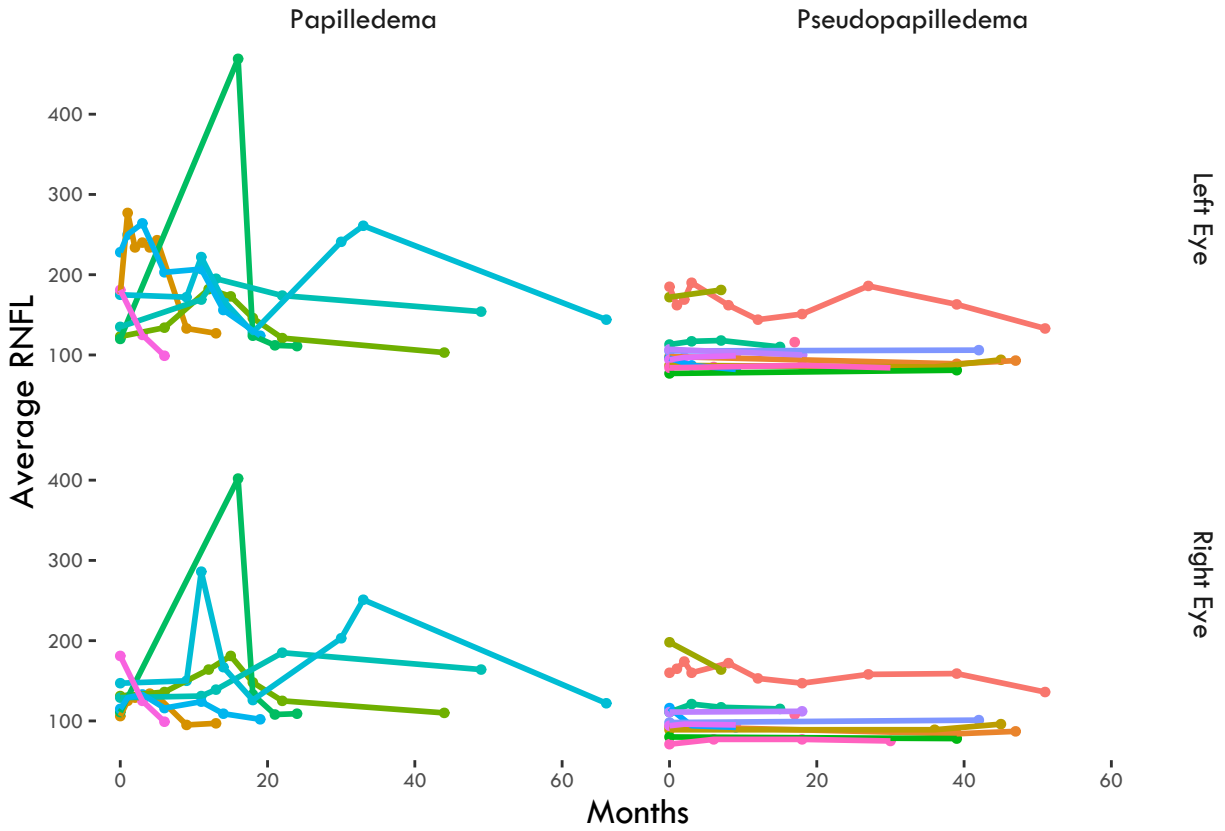
We can examine the distributions of the inferior, superior, nasal and temporal retinal nerve fibre layer thicknesses (RNFL.I, RNFL.S, RNFL.N, RNFL.T) in patients with Papilledema vs. those with Psuedopapilledema. The distributions of all these measurements show a similar pattern of Papilledema values being skewed to higher values. The superior retinal nerve fibre layer thickness shows one value which appears to be an outlier.



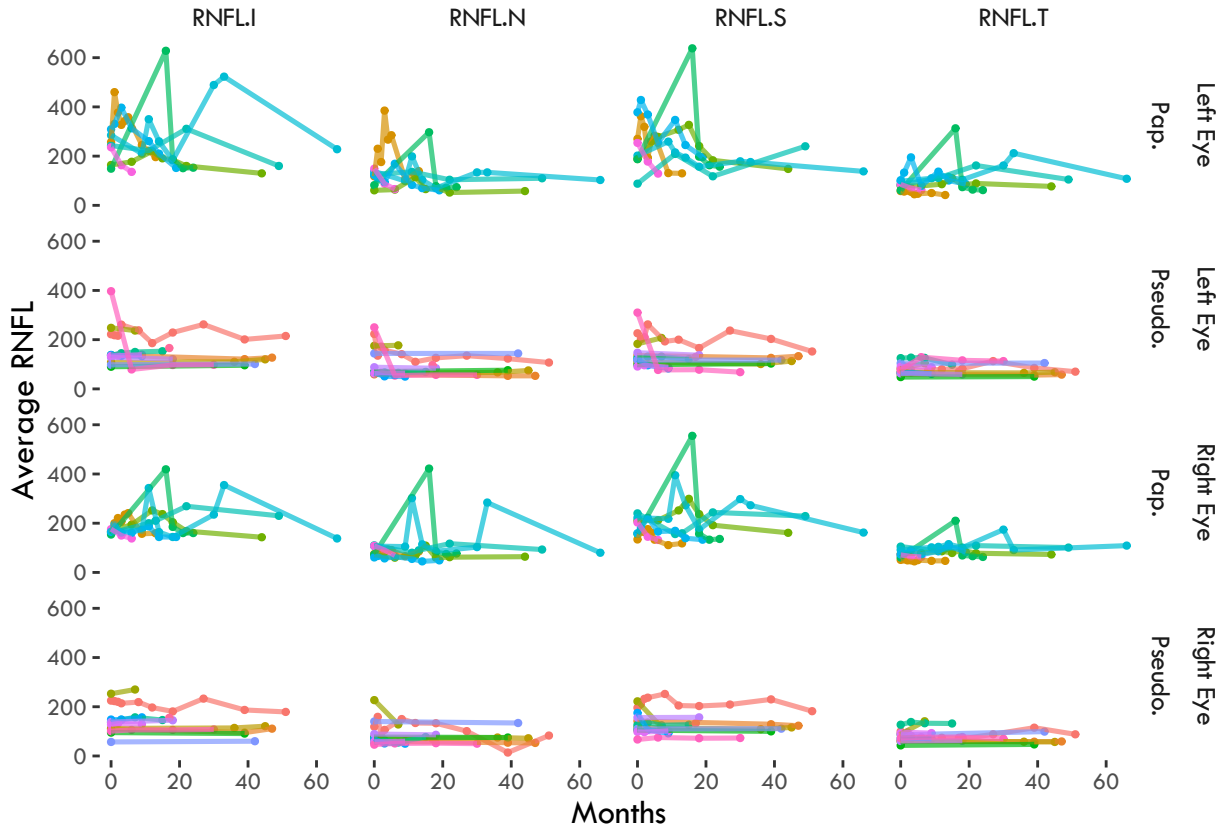
Boxplots better illustrate the difference in variance of the these measures for Papilledema vs. Psuedopapilledema patients. The outlier was removed so that the distributions could be better compared side by side. For each retinal measurement the median value is generally higher for Papilledema patients vs. Pseudopapilledema. The range of values is also much greater for Papilledema patients.



The trends in average RNFL thickness are examined by charting the values over time for each patient. The range in values for average RNFL thickness is much greater for Papilledema patients than Pseudopapilledema. The RNFL values of each Pseudopapilledema patient stay within a relatively narrow range over time. The one outlier was removed.



We can examine the sames trends for each individual RNFL measurement. The pattern is similar to the average RNFL for each measurement. There's a much greater amount of variation between each measurement over time for the Papilledema patients compared to the Pseudopapilledema patients.



##**Feature Engineering**

- Roll up measures to the patient level - for example left_RNFL.I will be a feature - one feature for each eye retinal length measure for all months (average?), also max min perhaps, number of visits, total time between first and last visit etc. Might require some programming.
- t-tests on these features.
- random forest - even though there are 19 Pseudo and 7 Pap maybe this would be useful?
- Logistic regression?
- A spreadsheet or application in which a doctor can enter these measures and a probability of Pap is returned?

#**Parametric Tests**

```
##
##  Welch Two Sample t-test
##
## data:  x.Psuedo and y.Pap
## t = -2.8574, df = 11.932, p-value = 0.0145
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##  -91.40192 -12.28640
## sample estimates:
## mean of x mean of y
##  110.7273  162.5714
```

```
## [1] 12
```

#**Machine Learning**

#**References**