SPAN Stage One Report - Early vs Late Metrics

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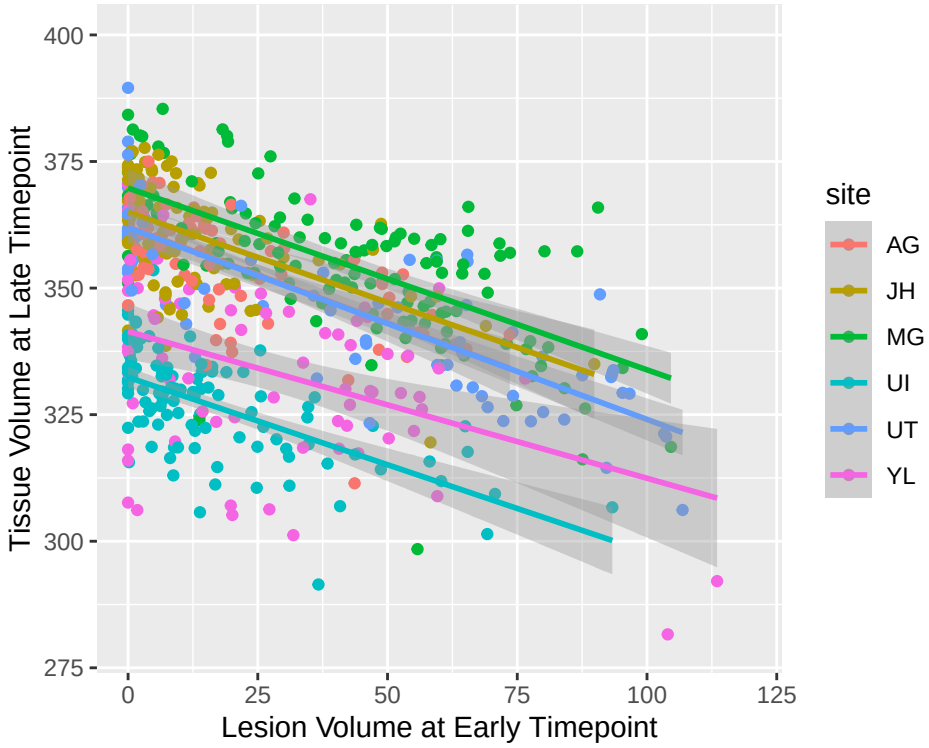
2021-06-09

This report investigates the relationship between early timepoint lesion volume and late timepoint atropy. We examine the general relationship and further refine the analysis by accounting for inter-site differences and also by refining the analysis to look at hemisphere-specific atropy measures.

Does early timepoint lesion predict late timepoint atropy?

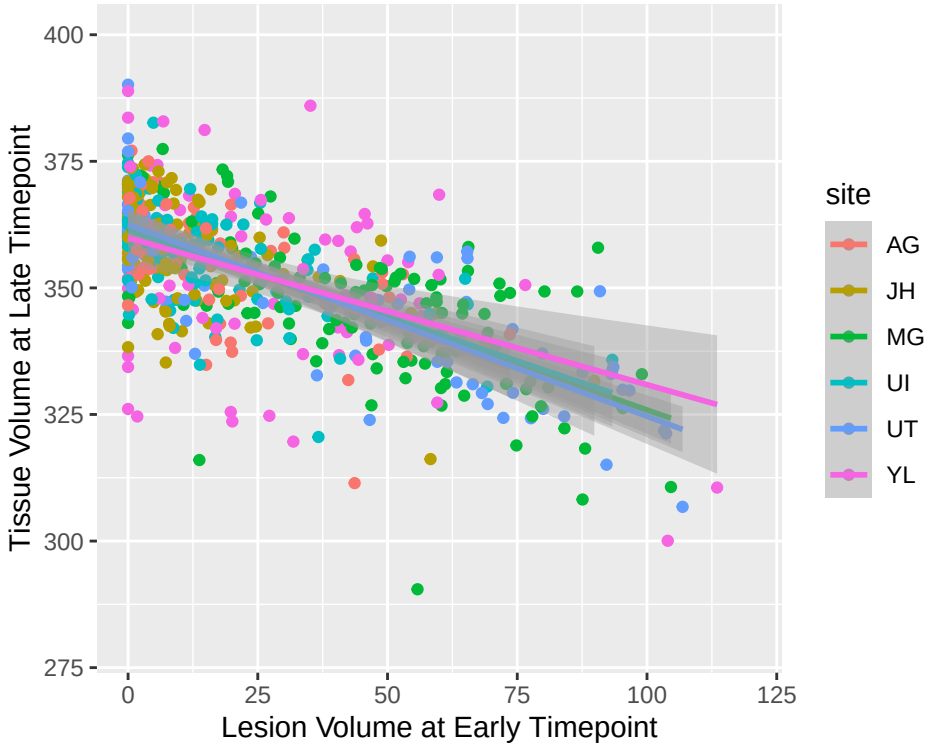
An initial test shows a strong relationship between early timepoint and late tissue volume (whole brain). There are clearly inter-site differences in total brain volume at the late timepoint, so let's incorporate that into the model and see how that improves things.




```
##
## Call:
## lm(formula = late_tissue ~ early_lesion, data = compare.df)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -52.641 -12.814   3.453  12.775  36.064
##
## Coefficients:
##               Estimate Std. Error t value Pr(>|t|)
## (Intercept)  353.48784    0.98924 357.332   <2e-16 ***
## early_lesion  -0.25597    0.02617  -9.782   <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 17.06 on 575 degrees of freedom
## Multiple R-squared:  0.1427, Adjusted R-squared:  0.1412
## F-statistic: 95.68 on 1 and 575 DF,  p-value: < 2.2e-16
```

When we correct for inter-site differences, how does early timepoint lesion predict late timepoint atropy?

We see that the inter-site differences are a major source of variance, and simplying adding the site as a covariate improves the model dramatically, increasing the R2 from 0.142 to 0.67. The slopes look similar, but next, let's check that by adding interaction by site.




```
##
## Call:
## lm(formula = late_tissue ~ early_lesion + site, data = compare.df)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -51.343  -5.983   0.834   6.763  36.831
##
## Coefficients:
##               Estimate Std. Error t value Pr(>|t|)
## (Intercept)  361.65106    1.21191 298.415  < 2e-16 ***
## early_lesion  -0.35549    0.01816 -19.578  < 2e-16 ***
## siteJH         3.32887    1.56177   2.131   0.0335 *
## siteMG         7.96041    1.55819   5.109 4.43e-07 ***
## siteUI       -29.09954    1.54481 -18.837  < 2e-16 ***
## siteUT        -0.58592    1.68993  -0.347   0.7289
## siteYL       -18.44731    1.69730 -10.869  < 2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 10.54 on 570 degrees of freedom
## Multiple R-squared:  0.6753, Adjusted R-squared:  0.6719
## F-statistic: 197.6 on 6 and 570 DF,  p-value: < 2.2e-16
```

Are there site-specific rates for early timepoint lesion predict late timepoint atropy?

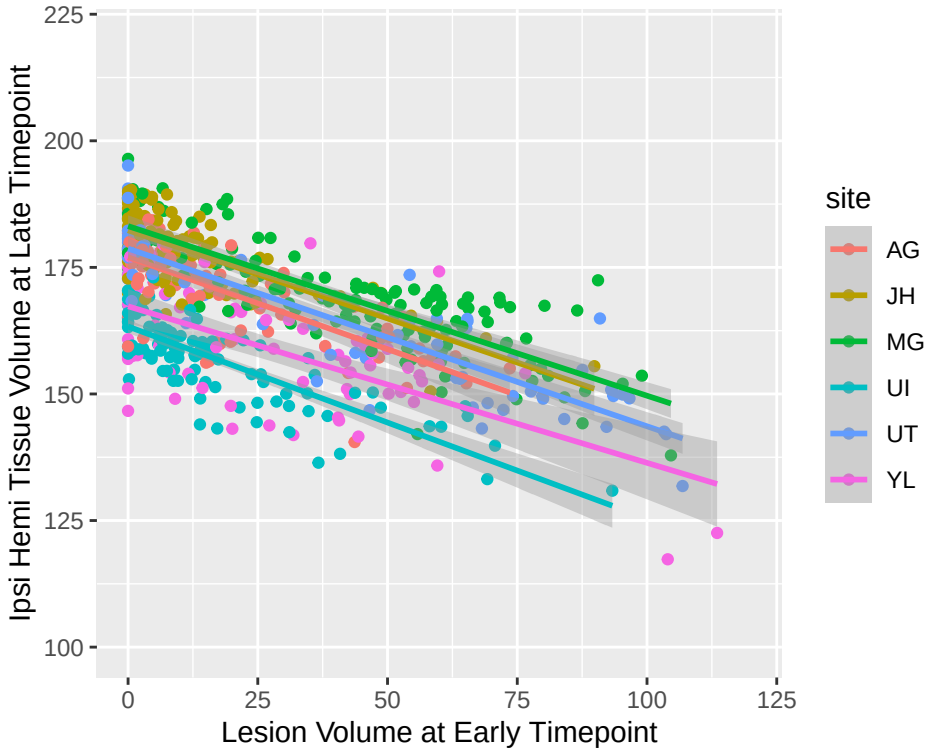
When including the interaction term, the model doesn't improve in adjusted R2, and non of the interactions are significant, so we can safely say that all of the sites have a similar relationship between early timepoint lesion and late timepoint tissue volume.

This analysis has only looked at whole brain tissue volume, so next we can look at hemisphere-specific effects.

```
##
## Call:
## lm(formula = late_tissue ~ early_lesion * site, data = compare.df)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -51.297  -6.006   0.788   7.050  36.296
##
## Coefficients:
##                         Estimate Std. Error t value Pr(>|t|)
## (Intercept)          362.101092   1.611339 224.721  < 2e-16 ***
## early_lesion          -0.379765   0.059942  -6.336 4.83e-10 ***
## siteJH                 2.888917   2.061954   1.401  0.16175
## siteMG                 7.667492   2.423117   3.164  0.00164 **
## siteUI               -29.708792   2.104365 -14.118  < 2e-16 ***
## siteUT                -0.249971   2.349678  -0.106  0.91531
## siteYL               -20.662513   2.430296  -8.502  < 2e-16 ***
## early_lesion:siteJH    0.023423   0.088179   0.266  0.79062
## early_lesion:siteMG    0.020624   0.069918   0.295  0.76812
## early_lesion:siteUI    0.034135   0.081555   0.419  0.67570
## early_lesion:siteUT    0.004384   0.067781   0.065  0.94846
## early_lesion:siteYL    0.089742   0.077910   1.152  0.24986
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 10.57 on 565 degrees of freedom
## Multiple R-squared:  0.6766, Adjusted R-squared:  0.6703
## F-statistic: 107.5 on 11 and 565 DF,  p-value: < 2.2e-16
```

Looking at only the isilateral hemisphere, how does early timepoint lesion predict late timepoint atropy?

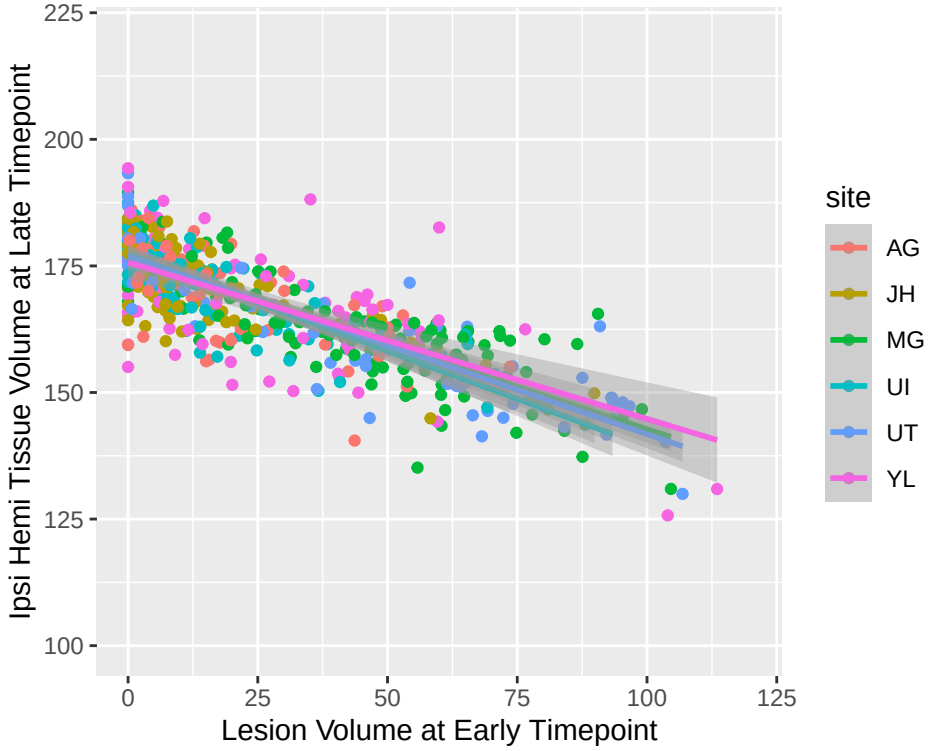
Looking first at the hemisphere ipsilateral to the lesion, we found a similar trend, but with an increased R2. What about again controlling for inter-site differences?




```
##
## Call:
## lm(formula = late_midline_right ~ early_lesion, data = compare.df)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -27.694  -7.156   1.559   7.427  24.409
##
## Coefficients:
##               Estimate Std. Error t value Pr(>|t|)
## (Intercept)  174.35212    0.58773  296.65   <2e-16 ***
## early_lesion  -0.29053    0.01555  -18.69   <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 10.13 on 575 degrees of freedom
## Multiple R-squared:  0.3778, Adjusted R-squared:  0.3768
## F-statistic: 349.2 on 1 and 575 DF,  p-value: < 2.2e-16
```

Looking at only the isilateral hemisphere and controlling for inter-site differences, how does early timepoint lesion predict late timepoint atropy?

Again, we find that inter-site differences in brain volume are a major contributor to the variance, but a covariate can control this quite well. The overall R2 has increased from 0.67 to 0.73. Next, let's look at the side contralateral to the lesion.

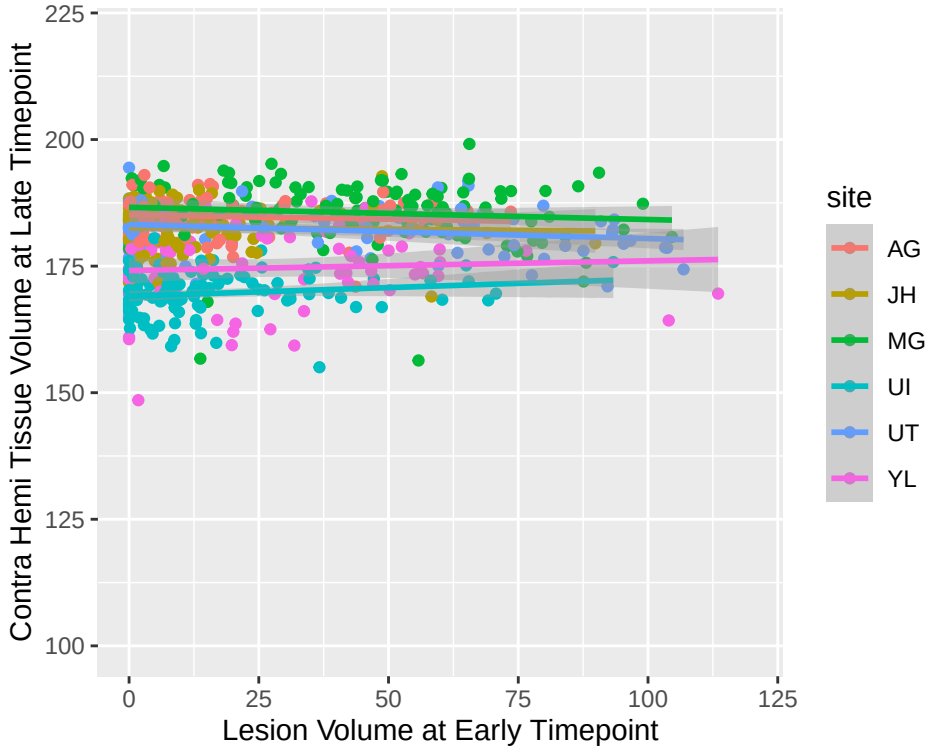



```
##
## Call:
## lm(formula = late_midline_right ~ early_lesion + site, data = compare.df)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -22.2702  -4.1505   0.6929   4.4052  26.5940
##
## Coefficients:
##               Estimate Std. Error t value Pr(>|t|)
## (Intercept)  176.65503    0.76201 231.827  < 2e-16 ***
## early_lesion  -0.34464    0.01142 -30.186  < 2e-16 ***
## siteJH         5.62748    0.98200   5.731 1.62e-08 ***
## siteMG         6.91200    0.97975   7.055 5.03e-12 ***
## siteUI       -13.89266    0.97133 -14.303  < 2e-16 ***
## siteUT         1.83998    1.06258   1.732   0.0839 .
## siteYL        -8.38589    1.06721  -7.858 1.96e-14 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 6.629 on 570 degrees of freedom
## Multiple R-squared:  0.7361, Adjusted R-squared:  0.7333
```

```
## F-statistic:   265 on 6 and 570 DF,  p-value: < 2.2e-16
```

Looking at only the contralateral hemisphere, how does early timepoint lesion predict late timepoint atropy?

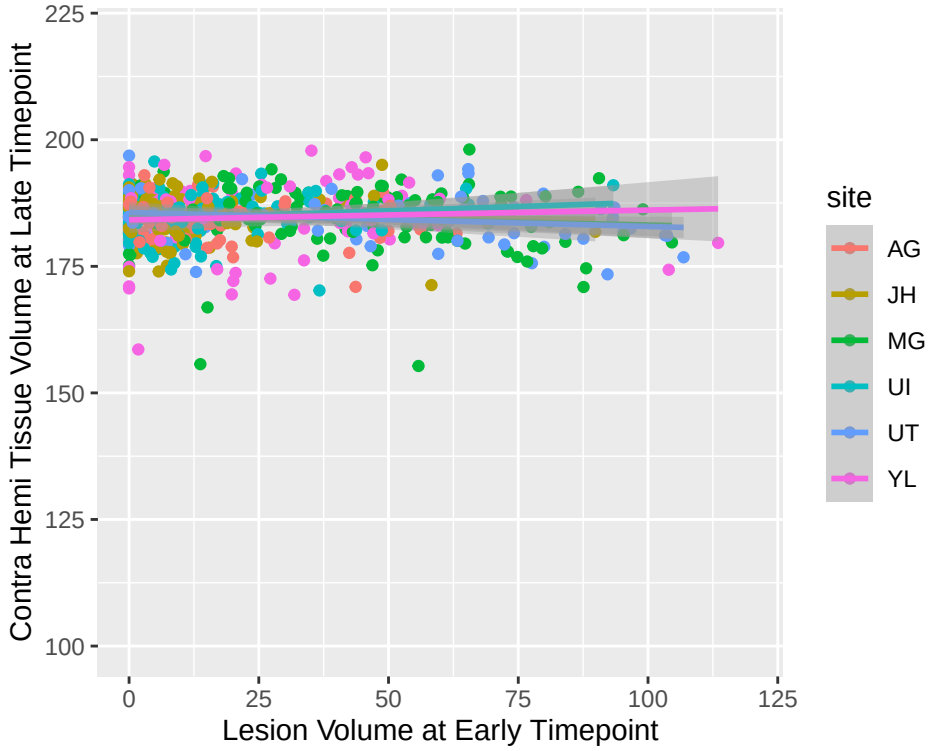
When looking at tissue volume on the hemisphere contralateral to the lesion, we see that there is now no relation relationship between early timepoint lesion volume and late timepoint tissue volume, suggesting that the atrophy is localized to the ispilateral side.




```
##
## Call:
## lm(formula = late_midline_left ~ early_lesion, data = compare.df)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -30.679  -5.455   1.458   5.771  17.728
##
## Coefficients:
##               Estimate Std. Error t value Pr(>|t|)
## (Intercept)  179.13574    0.45844  390.75  < 2e-16 ***
## early_lesion   0.03456    0.01213    2.85  0.00453 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 7.904 on 575 degrees of freedom
## Multiple R-squared:  0.01393,    Adjusted R-squared:  0.01221
## F-statistic: 8.121 on 1 and 575 DF,  p-value: 0.004533
```

Looking at only the contralateral hemisphere and controlling for inter-site differences, how does early timepoint lesion predict late timepoint atropy?

We further confirm this finding by including a covariate for site.




```
##
## Call:
## lm(formula = late_midline_left ~ early_lesion + site, data = compare.df)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -29.1733  -2.6685   0.4958   3.2167  13.7973
##
## Coefficients:
##                Estimate Std. Error t value Pr(>|t|)
## (Intercept)  184.996033   0.603696 306.439  < 2e-16 ***
## early_lesion  -0.010852   0.009045  -1.200  0.23071
## siteJH        -2.298580   0.777977  -2.955  0.00326 **
## siteMG         1.048370   0.776193   1.351  0.17734
## siteUI       -15.206833   0.769525 -19.761  < 2e-16 ***
## siteUT        -2.425874   0.841816  -2.882  0.00410 **
## siteYL       -10.061479   0.845485 -11.900  < 2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 5.252 on 570 degrees of freedom
## Multiple R-squared:  0.5685, Adjusted R-squared:  0.564
## F-statistic: 125.2 on 6 and 570 DF,  p-value: < 2.2e-16
```