# Vector generalized linear model applied to cortical thickness in neurodegenerative disease follow-up

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## BACKGROUND

In neurodegenerative diseases, cognitive impairments are closely related to neuron loss. One of image based biomarkers of this loss is the cortical thickness (CTh). Usually, longitudinal studies on disease course are focused on testing cortical thickness differences among different stages of the disease progression. There are few studies that analyze the influence of the cortical thinning on the evolution of the disease, i.e. which consider this thinning as variable explaining cognitive disorders.

## GOAL

Our aim was to test an original method which should help to understand the influence of neuronal loss on the evolution of the pathology.

## MATERIALS AND METHODS

**Subjects:** 136 subjects from the ADNI database (Alzheimer's Disease Neuroimaging Initiative) were included in our study. Our population was composed of normal subjects (HC), Alzheimer's disease patients (AD) and progressive mild cognitive impairment patients (pMCI) who will convert during the follow-up.
All groups are paired in age, both in mean ($F(3, 132)=0.7$, $p=0.55$) and in variance (Levene's test $F(3, 132)=1.1$, $p=0.35$).

**Follow-up:** Every subject received a baseline clinical evaluation and was re-evaluated after inclusion, over a total period of 36 months.

**Imaging modality:** MRI-T1 images at 1.5 Tesla.

**Measurement of cortical thickness:** The CTh was measured in 24 cortical areas using the Toolbox Matlab® CorThiZon developed in the INSERM U1214 ToNIC laboratory.

**Method:** We aimed to characterize the evolution of the pathology degree by a particular spatial profile. Therefore, we have focused our analysis on relations between the pMCI spatio-temporal evolution of the CTh and the evolution of the pathology by using a vector generalized linear model (VGLM).
Ordinal logistic regression is a classical technique for analyzing the dependencies between an ordinal dependent variable, in our case, the degree of pathology (figure1) and independent variables, which are here the CTh of the 24 areas.

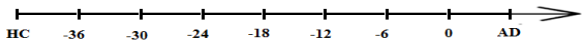


**Figure1 - Ordinal dependant variable – The degree of pathology**

**-6, -12, -18, -24, -30, -36 : Months before conversion to AD ("0" represent the conversion moment)**

Continuation-ratios are suitable to assess whether cortical thinning, in a given cortical area, is related to the disease progression. Thus, we have decided to model the probability of stopping pathological cognitive impairments at a given stage, given that this stage is yet reached. We tested each areas one after the other, so we have emphasized the gross influence of each area independently of the others.

## RESULTS

| Significant areas \ DATE | HC | -36 | -30 | -24 | -18 | -12 | -6 | 0 |
|---|---|---|---|---|---|---|---|---|
| Posterior Cingulate_L | 2.11 *** | | | | | | *1.51* · | |
| Mesial Temporal_L | 6.52 *** | 5.33 *** | 5.18 *** | 4.95 *** | 5.28 *** | 5.68 *** | 5.63 *** | 5.13 *** |
| Mesial Temporal_R | -2.63 ** | -4.51 ** | -4.75 ** | -4.64 *** | -4.22 *** | -3.91 *** | -4.13 *** | -4.51 *** |
| Parietal_R | -1.58 * | *-2.21* · | -2.25 · | -2.22 * | -1.99 * | *-1.55* · | *-1.71* · | -2.06 * |
| Dorsolateral prefrontal_L | 2.16 ** | | | | | 1.99 * | 2.13 * | 1.99 * |
| Temporal Lateral_L | | | | | | | | -1.36 * |
| Temporal Lateral_R | 1.94 ** | | | | 1.56 * | 1.61 * | 1.54 * | |

Positive coefficient = stabilization at the corresponding level

Negative coefficient = evolution towards a higher stage

Not significant

Codes of significance: '***' $p<0.001$ ; '**' $0.001<p<0.01$ ; '*' $0.01<p<0.05$ ; '·' $0.1<p<1$

**Table representing the estimated values in the case of a significance for the model which tests the probability of the progression interruption at a given level i, knowing that it has already been reached**

**DATE: Ordinal dependant variable - The degree of pathology**

- The left posterior cingulate plays a major stabilization role in the state of normal aging (HC) ($p<0.001$).
- The left mesial-temporal plays a very important role in the MCI stabilization ($p<0.001$).
- Frontal and temporal areas are the most involved in the stabilization around the conversion.
- Right and left temporal areas have different models $\Rightarrow$ Marker of right/left symmetry loss in the evolution to AD.

## DISCUSSION AND CONCLUSION

**Conclusion:** The left posterior cingulate is an early marker of Alzheimer's disease, as described in the literature. Thus, we think that the vglm approach is a promising approach, which provides additional information to more traditional analyses such as regression or Anova analyses and survival analyses. Such, this approach should find its place in the range of methods of analysis focused on pathology evolution .

**Comparison to survival analysis:** The vglm approach is linked to survival analysis although it differs at least in the following three points:

- Survival analysis focuses on conditions inducing an event such as the conversion to probable AD while the vglm approach is interested in the stabilization of the patient's status;
- In the context of survival analysis, the absence of the event is considered to be censored data while the vglm approach allows to estimate the conditions that prevent the occurrence of this event, at least, within a future equivalent to the duration of the study;
- The vglm approach easily allows to analyze disease progression beyond the event in question while more complicated approaches such as multiple failure time are required for survival analysis.

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**Reference:** Yee TW (2008) , *The VGAM package for categorical data analysis*, Journal of Statistical Software 32 (10) 1-34.