Estimating cognitive trajectory and the changing effect of pathologies using a nonparametric time-varying effect model

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Manuscript in progress
Different longitudinal data

### Traditional longitudinal data
- Limited # of measurements
- Incapable of revealing
  - irregular ups and downs
  - temporal association or
time-varying effects

### Intensive longitudinal data (ILD)
- Irregular time series
  - Partially missing
  - Unequally spaced
- Many observations at each
time points
Collection of ILD

- Web-based assessment
- Hand-held computers (e.g., PDA)
- Other portable devices (actigraph, GPS, iWatch, iPhone)
- Data collected from well-designed longitudinal studies that have a long time of follow-ups (e.g., data from ROSMAP)
Time-varying effect model: A motivating example
The time-varying effect model (TVEM)

- Does not impose a parametric form on the coefficient functions
- Can accurately reveal the underlying shape of coefficient functions
- Capable of handling different responses
  - Continuous
  - Binary
  - Poisson
  - ZIP
- User-friendly and easy-to-implement SAS macro suite

Using TVEM to examine cognitive trajectory

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>N</td>
<td>641</td>
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<tr>
<td>Study</td>
<td>ROS (n=339)/MAP (n=302)</td>
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<tr>
<td>Follow-up, mean (range)</td>
<td>9.3 (4-19)</td>
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<tr>
<td>Age at death</td>
<td>89.7±6.3</td>
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<tr>
<td>Gender, male</td>
<td>31.8%</td>
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<tr>
<td>Education</td>
<td>16.4±3.6</td>
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<tr>
<td>Global pathology</td>
<td>0.6±0.7</td>
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<tr>
<td>Lewy bodies</td>
<td>23.9%</td>
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<tr>
<td>Hippocampal sclerosis</td>
<td>12.6%</td>
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<tr>
<td>Arteriolar sclerosis</td>
<td>30.9%</td>
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<tr>
<td>Gross chronic cerebral Infarcts</td>
<td>0.4±0.5</td>
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<tr>
<td>Gross subacute cerebral Infarcts</td>
<td>0.1±0.3</td>
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<tr>
<td>Gross acute cerebral Infarcts</td>
<td>0.1±0.3</td>
</tr>
<tr>
<td>Cerebral amyloid angiopathy</td>
<td>1.1±1.0</td>
</tr>
<tr>
<td>TDP-43</td>
<td>0.6±1.0</td>
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</tbody>
</table>
Using TVEM to examine cognitive trajectory

- Outcome: global cognition
- Adjust for sex, education, age at death, APOE4
- Type of coefficients:
  - Time-invariant: sex, education, age at death
  - Time-varying: APOE, pathologies
- Time: time to death
- Strategy:
  - Examine each pathology individually
  - Examine all pathologies simultaneously
Using TVEM to examine cognitive trajectory: sample code

%TVEM_normal(method=B-spline,
mydata=e4_path_all_mod,
id=projid_new,
time=cog2die,
dep=cogn_global,
class_var=msex,
tcov=x0 anye4 gpath,
cov=msex educ16 age_death_c,
cov_knots=6 6 6
);
Cognitive trajectory and effect of APOE and pathologies: individual examination

Mean trajectory

APOE4

Global pathology

TDP-43
Cognitive trajectory and effect of APOE and pathologies: individual examination

- Lewy bodies
- Hippocampal sclerosis
- Arteriolar sclerosis
- Cerebral atherosclerosis
Cognitive trajectory and effect of APOE and pathologies: individual examination

- **Gross chronic cerebral infarcts**
- **Gross subacute cerebral infarcts**
- **Gross acute cerebral infarcts**
- **Cerebral amyloid angiopathy**
Cognitive trajectory and effect of APOE and pathologies: simultaneous examination

**Mean trajectory**

**APOE4**

**Global pathology**

**TDP-43**
Cognitive trajectory and effect of APOE and pathologies: simultaneous examination

- Lewy bodies
- Hippocampal sclerosis
- Arteriolar sclerosis
- Cerebral atherosclerosis
Cognitive trajectory and effect of APOE and pathologies: simultaneous examination

Gross chronic cerebral infarcts

Gross acute cerebral infarcts

Gross subacute cerebral infarcts

Cerebral amyloid angiopathy
Comparison of the time-varying effect:

**Individual**

**Simultaneous**

Global pathology
Comparison of the time-varying effect:

**Individual**

**Simultaneous**

APOE4
Comparison of the time-varying effect:

Individual

Simultaneous

TDP-43
Summary of results

- Older adults experienced gradual cognitive decline along aging, and sharp decline before death (terminal decline)
- Pathologies exerted effect on cognition about 10 years before death
- The effect of APOE is similar as pathologies
- After controlling for other pathologies, the effect of APOE on cognition is only minimally significant in the 4 years before death
- Cerebral infarcts had little effect on cognition over time, after controlling for other pathologies
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