New LME Model

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1 Model

We include all subjects (188 AD, 147 amyloid-positive MCI, 43 amyloid-positive healthy controls) in the model. Denote time by t, age by a, gender by g, education by e, and ICV over GM by i. We have two binary indicators, d for AD and m for MCI, at most one of which is 1. Neither being 1 implies that the subject is a normal control. We consider $K = 3$, and we include subcortical factor probability s and cortical factor probability c in the model, implicitly modeling the temporal factor as the reference factor. For simplicity, we investigate the memory score y_m while controlling for the executive function score y_e.

For a subject's one timepoint, the LME model is as follows.

$$
\begin{aligned}
y_m &= X\beta + Zb + \epsilon && (1)\\
&= [&& (2)\\
&1 \quad m \quad d \quad s \quad c \quad ms \quad mc \quad ds \quad dc && (3)\\
&t \quad mt \quad dt \quad st \quad ct \quad mst \quad mct \quad dst \quad dct && (4)\\
&a \quad g \quad e \quad i \quad y_e && (5)\\
&]\beta && (6)\\
&+ [1]b && (7)\\
&+ \epsilon, && (8)
\end{aligned}
$$

where for example, β_t, coefficient for term t, is the normal temporal factor's decline rate in memory.

We spell out the following “pure-factor” cases:

+ signs between β’s are omitted for convenience.

normal temporal	β_1									$t\cdot($	β_t									$)$
normal subcortical	β_1			β_s						$t\cdot($	β_t			β_{st}						$)$
normal cortical	β_1				β_c					$t\cdot($	β_t				β_{ct}					$)$
MCI temporal	β_1	β_m								$t\cdot($	β_t	β_{mt}								$)$
MCI subcortical	β_1	β_m		β_s		β_{ms}				$t\cdot($	β_t	β_{mt}		β_{st}		β_{mst}				$)$
MCI cortical	β_1	β_m			β_c		β_{mc}			$t\cdot($	β_t	β_{mt}			β_{ct}		β_{mct}			$)$
AD temporal	β_1		β_d							$t\cdot($	β_t		β_{dt}							$)$
AD subcortical	β_1		β_d	β_s				β_{ds}		$t\cdot($	β_t		β_{dt}	β_{st}				β_{dst}		$)$
AD cortical	β_1		β_d		β_c				β_{dc}	$t\cdot($	β_t		β_{dt}		β_{ct}				β_{dct}	$)$

2 Hypothesis Testing

2.1 Within Stages, Between Factors

We only list out baseline comparisons for brevity.

Omnibus test: do factors have the same baseline scores within each cohort?

- Normal: test if $\beta_s = \beta_c = 0$.
- MCI: test if $\beta_c + \beta_{mc} = \beta_s + \beta_{ms} = 0$.
- AD: test if $\beta_c + \beta_{dc} = \beta_s + \beta_{ds} = 0$.

Do temporal and subcortical factors have the same baseline scores?

- Normal: test if $\beta_s = 0$.
- MCI: test if $\beta_s + \beta_{ms} = 0$.
- AD: test if $\beta_s + \beta_{ds} = 0$.

Do temporal and cortical factors have the same baseline scores?

- Normal: test if $\beta_c = 0$.
- MCI: test if $\beta_c + \beta_{mc} = 0$.
- AD: test if $\beta_c + \beta_{dc} = 0$.

Do subcortical and cortical factors have the same baseline scores?

- Normal: test if $\beta_s = \beta_c$.
- MCI: test if $\beta_s + \beta_{ms} = \beta_c + \beta_{mc}$.
- AD: test if $\beta_s + \beta_{ds} = \beta_c + \beta_{dc}$.

2.2 Across Stages, Within Factors

The following comparisons help plot the factor trajectories.

1. Does the temporal factor maintain the same decline rate from the normal stage to MCI? Test if $\beta_{mt} = 0$. From MCI to AD? Test if $\beta_{dt} = \beta_{mt}$.
2. Does the subcortical factor maintain the same decline rate from the normal stage to MCI? Test if $\beta_{mt} + \beta_{mst} = 0$. From MCI to AD? Test if $\beta_{mt} + \beta_{mst} = \beta_{dt} + \beta_{dst}$.
3. Does the cortical factor maintain the same decline rate from the normal stage to MCI? Test if $\beta_{mt} + \beta_{mct} = 0$. From MCI to AD? Test if $\beta_{mt} + \beta_{mct} = \beta_{dt} + \beta_{dct}$.

2.3 Other Interesting Questions

1. (Sanity check) Do stages affect decline rates? Normal temporal equal to MCI temporal requires $\beta_{mt} = 0$, and normal subcortical equal to MCI subcortical requires $\beta_{mt} + \beta_{mst} = 0$. Therefore, $\beta_{mst} = 0$. Ultimately, the test is $\beta_{mt} = \beta_{dt} = \beta_{mst} = \beta_{mct} = \beta_{dst} = \beta_{dct} = 0$.

2. (Overall test for the forrest plots) Do factors affect decline rates? Test if $\beta_{st} = \beta_{ct} = \beta_{mst} = \beta_{mct} = \beta_{dst} = \beta_{dct} = 0$.

3. Do factors affect decline rates differently at different stages? Comparing normal and MCI subcortical, we have $\beta_{mst} = 0$. Comparing MCI and AD subcortical, we have $\beta_{mst} = \beta_{dst}$. Ultimately, the test is $\beta_{mst} = \beta_{dst} = \beta_{mct} = \beta_{dct} = 0$

Appendix A $K = 2$

$$
\begin{aligned}
y_m &= X\beta + Zb + \epsilon && (9)\\
&= [&& (10)\\
& 1 \quad m \quad d \quad c \quad mc \quad dc && (11)\\
& t \quad mt \quad dt \quad ct \quad mct \quad dct && (12)\\
& a \quad g \quad e \quad i \quad y_e && (13)\\
&]\beta && (14)\\
&+ [1]b && (15)\\
&+ \epsilon, && (16)
\end{aligned}
$$

normal temporal+subcortical	β_1						$t \cdot ($	β_t						$)$
normal cortical	β_1			β_c			$t \cdot ($	β_t			β_{ct}			$)$
MCI temporal+subcortical	β_1	β_m					$t \cdot ($	β_t	β_{mt}					$)$
MCI cortical	β_1	β_m		β_c	β_{mc}		$t \cdot ($	β_t	β_{mt}		β_{ct}	β_{mct}		$)$
AD temporal+subcortical	β_1		β_d				$t \cdot ($	β_t		β_{dt}				$)$
AD cortical	β_1		β_d	β_c		β_{dc}	$t \cdot ($	β_t		β_{dt}	β_{ct}		β_{dct}	$)$

Appendix B $\quad K = 4$

$$
\begin{aligned}
y_m &= X\beta + Zb + \epsilon && (17)\\
&= [&& (18)\\
& 1 \quad m \quad d \quad s \quad f \quad p \quad ms \quad mf \quad mp \quad ds \quad df \quad dp && (19)\\
& t \quad mt \quad dt \quad st \quad ft \quad pt \quad mst \quad mft \quad mpt \quad dst \quad dft \quad dpt && (20)\\
& a \quad g \quad e \quad i \quad y_e && (21)\\
&]\beta && (22)\\
& + [1]b && (23)\\
& + \epsilon, && (24)
\end{aligned}
$$

CN T	β_1												$t \cdot ($	β_t												$)$
CN S	β_1			β_s									$t \cdot ($	β_t			β_{st}									$)$
CN F	β_1				β_f								$t \cdot ($	β_t				β_{ft}								$)$
CN P	β_1					β_p							$t \cdot ($	β_t					β_{pt}							$)$
MCI T	β_1	β_m											$t \cdot ($	β_t	β_{mt}											$)$
MCI S	β_1	β_m		β_s			β_{ms}						$t \cdot ($	β_t	β_{mt}		β_{st}			β_{mst}						$)$
MCI F	β_1	β_m			β_f			β_{mf}					$t \cdot ($	β_t	β_{mt}			β_{ft}			β_{mft}					$)$
MCI P	β_1	β_m				β_p			β_{mp}				$t \cdot ($	β_t	β_{mt}				β_{pt}			β_{mpt}				$)$
AD T	β_1		β_d										$t \cdot ($	β_t		β_{dt}										$)$
AD S	β_1		β_d	β_s						β_{ds}			$t \cdot ($	β_t		β_{dt}	β_{st}						β_{dst}			$)$
AD F	β_1		β_d		β_f						β_{df}		$t \cdot ($	β_t		β_{dt}		β_{ft}						β_{dft}		$)$
AD P	β_1		β_d			β_p						β_{dp}	$t \cdot ($	β_t		β_{dt}			β_{pt}						β_{dpt}	$)$