# Part [2.2]: Characterizing the Accuracy of Markers Used to Select Treatment


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# Magnetic resonance imaging compared with electrodiagnostic studies in patients with suspected carpal tunnel syndrome: predicting symptoms, function, and surgical benefit at 1 year.

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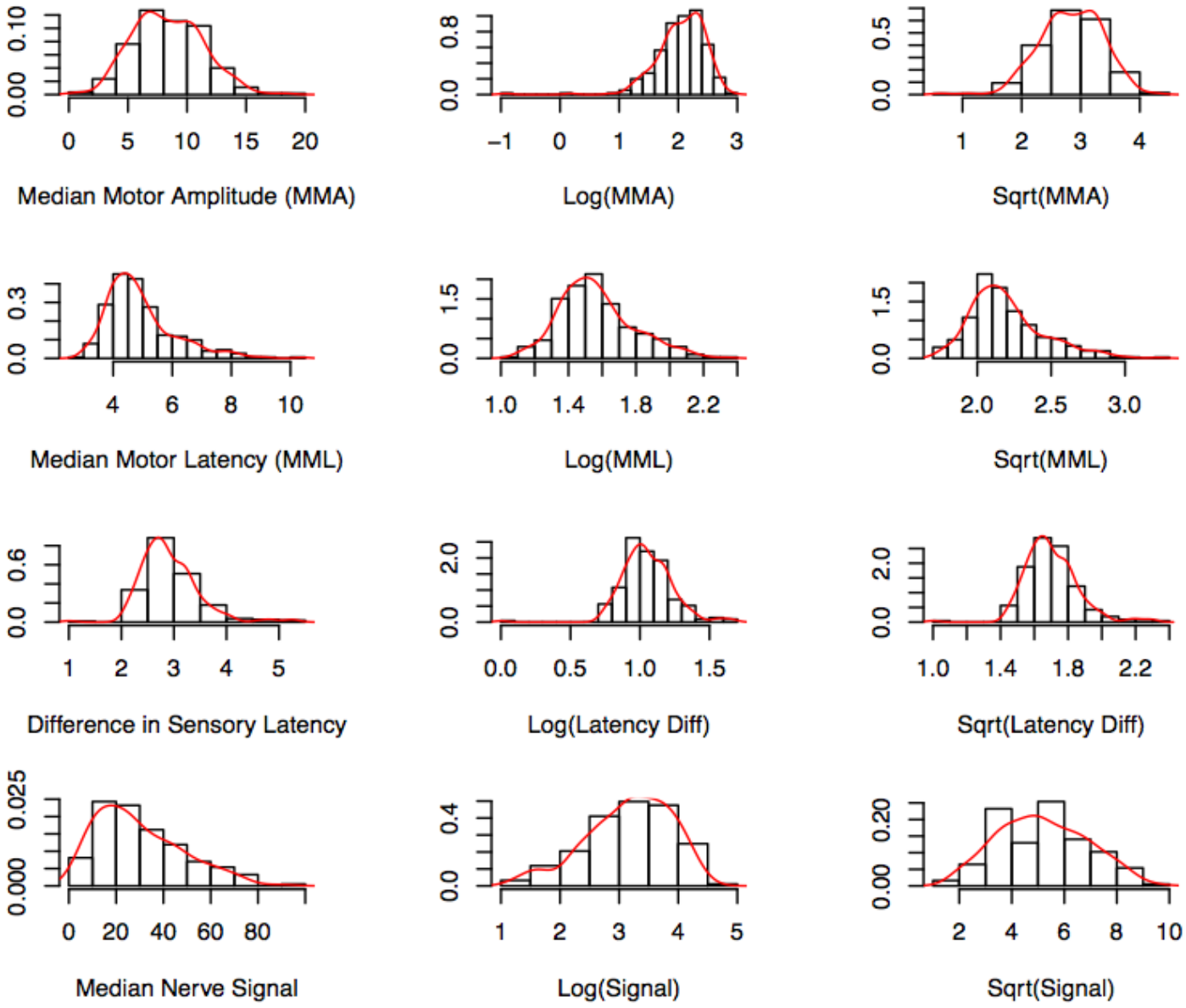
## Abstract

**OBJECT:** The goal in this study of patients with clinical carpal tunnel syndrome (CTS) was to compare the usefulness of magnetic resonance (MR) imaging with that of electrodiagnostic studies (EDSs) for the following purposes: 1) prediction of 1-year outcomes and 2) identification of patients who are likely to benefit from surgical treatment.

**METHODS:** The authors prospectively enrolled 120 patients with clinically suspected CTS. The participants were tested using standardized EDSs, MR imaging, and a battery of questionnaires, including the Carpal Tunnel Syndrome Assessment Questionnaire, a well-validated 5-point score of symptoms and function. The EDSs and MR images were each interpreted independently. Patients were reevaluated after 1 year. The decision to treat patients conservatively or by carpal tunnel release was made by the individual surgeon, who had access to the initial EDS but not MR imaging results. Univariate and multivariate analyses were used to determine associations between 1-year outcomes and baseline diagnostic tests.

**RESULTS:** The authors recontacted 105 of 120 participants at 12 months. Of these, 30 patients had had surgery and 75 had not. Patients who had undergone surgery showed greater improvement at 1 year than those who had not had surgery. The length of the abnormal T2-weighted nerve signal on MR imaging and median-ulnar sensory latency difference were the strongest predictors of surgical benefit. There was a clear patient preference for the MR imaging over EDSs.

**CONCLUSIONS:** The findings obtained with MR imaging of the carpal tunnel predict surgical benefit independently of nerve conduction studies.


0.00 0.10
0 5 10 15 20
Median Motor Amplitude (MMA)
0.0 0.8
−1 0 1 2 3
Log(MMA)
0.0 0.5
1 2 3 4
Sqrt(MMA)
0.0 0.3
4 6 8 10
Median Motor Latency (MML)
0.0 1.5
1.0 1.4 1.8 2.2
Log(MML)
0.0 1.5
2.0 2.5 3.0
Sqrt(MML)
0.0 0.6
1 2 3 4 5
Difference in Sensory Latency
0.0 2.0
0.0 0.5 1.0 1.5
Log(Latency Diff)
0.0 2.0
1.0 1.4 1.8 2.2
Sqrt(Latency Diff)
0.000 0.025
0 20 40 60 80
Median Nerve Signal
0.0 0.4
1 2 3 4 5
Log(Signal)
0.00 0.20
2 4 6 8 10
Sqrt(Signal)

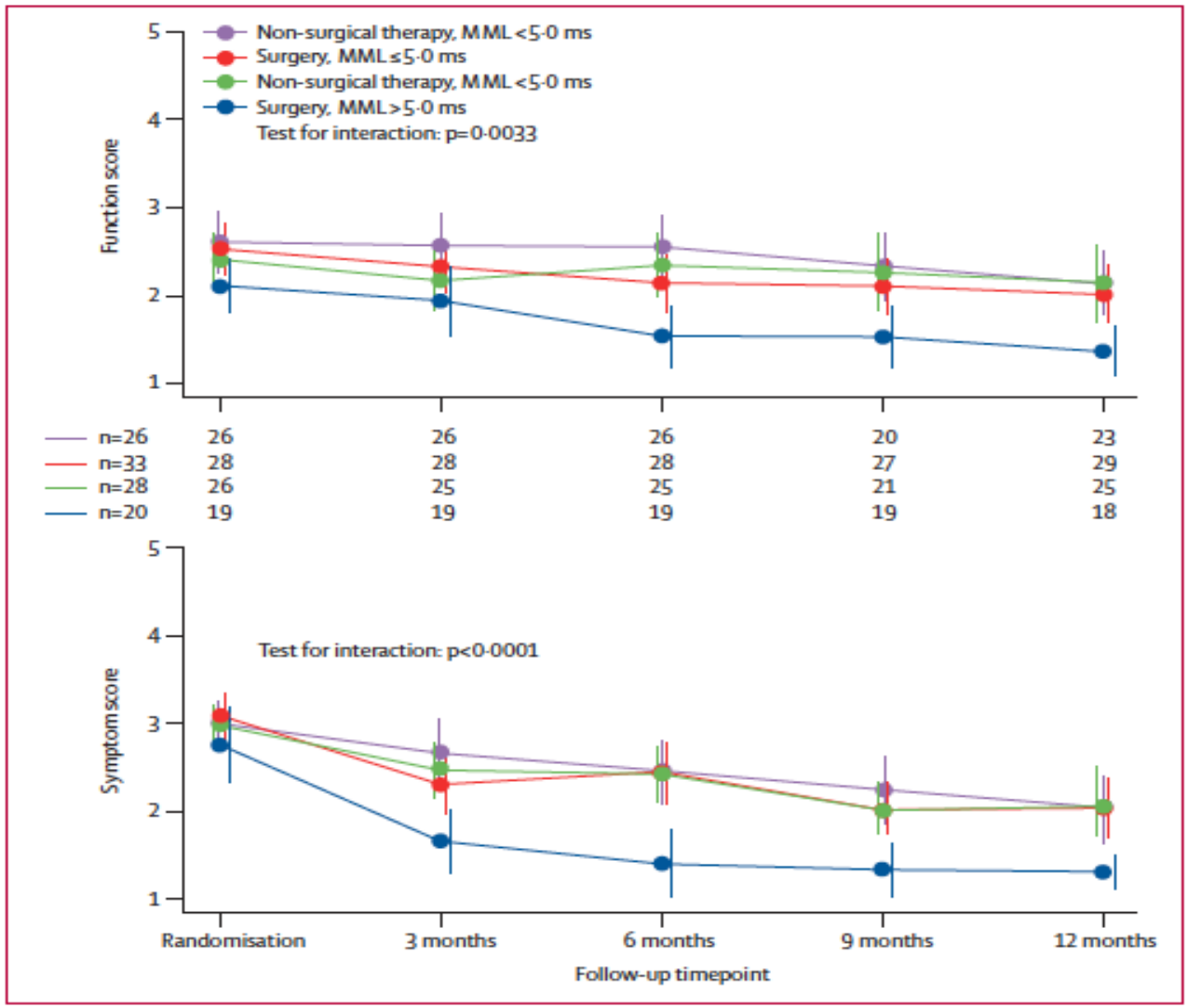



***Figure 2:*** **Carpal Tunnel Syndrome Assessment Questionnaire (CTSAQ) function and symptom scores**
Scores are stratified by randomised treatment assignment and baseline distal median motor latency. Data are mean (95% CI).

# Markers for Treatment Selection

- Motivation:
  - The **second** aim of an RCT is often to determine **who** will benefit from treatment.
  - Markers to guide treatment choice (decision)
  - Example: Carpal Tunnel / surgery / EDS and MRI
- Statistical Formulation:
  - Ability of markers to **classify**
  - Groups:

    **1** : patients with `TX` $>>$ `control`

    **0** : patients with `TX` $<<$ `control`

# Markers for Treatment Selection

- Typical data

| subject | treatment | control | $\Delta$ |
|---|---|---|---|
| 101 | $Y_i(1)$ | - | - |
| 102 | - | $Y_i(0)$ | - |

# Markers for Treatment Selection

- Desired information

| subject | treatment | control | $\Delta$ |
|---|---|---|---|
| 101 | $Y_i(1)$ | $Y_i(0)$ | $\Delta_i$ |
| 102 | $Y_i(1)$ | $Y_i(0)$ | $\Delta_i$ |

- "Principal strata" (Frangakis and Rubin, 2002)
- Janes et al. (2015) *JNCI*

# Markers for Treatment Selection

- If you had data: $(\Delta_i, M_i)$ for a marker $M_i$ then you could summarize:

$$\text{p-PPV} \quad : \quad P[\Delta_i > 0 \mid M_i > c]$$
$$\text{p-NPV} \quad : \quad P[\Delta_i \leq 0 \mid M_i \leq c]$$

$$\text{p-Sensitivity} \quad : \quad P[M_i > c \mid \Delta_i > 0]$$
$$\text{p-Specificity} \quad : \quad P[M_i \leq c \mid \Delta_i \leq 0]$$

- Here the prefix p- is for "prescriptive".

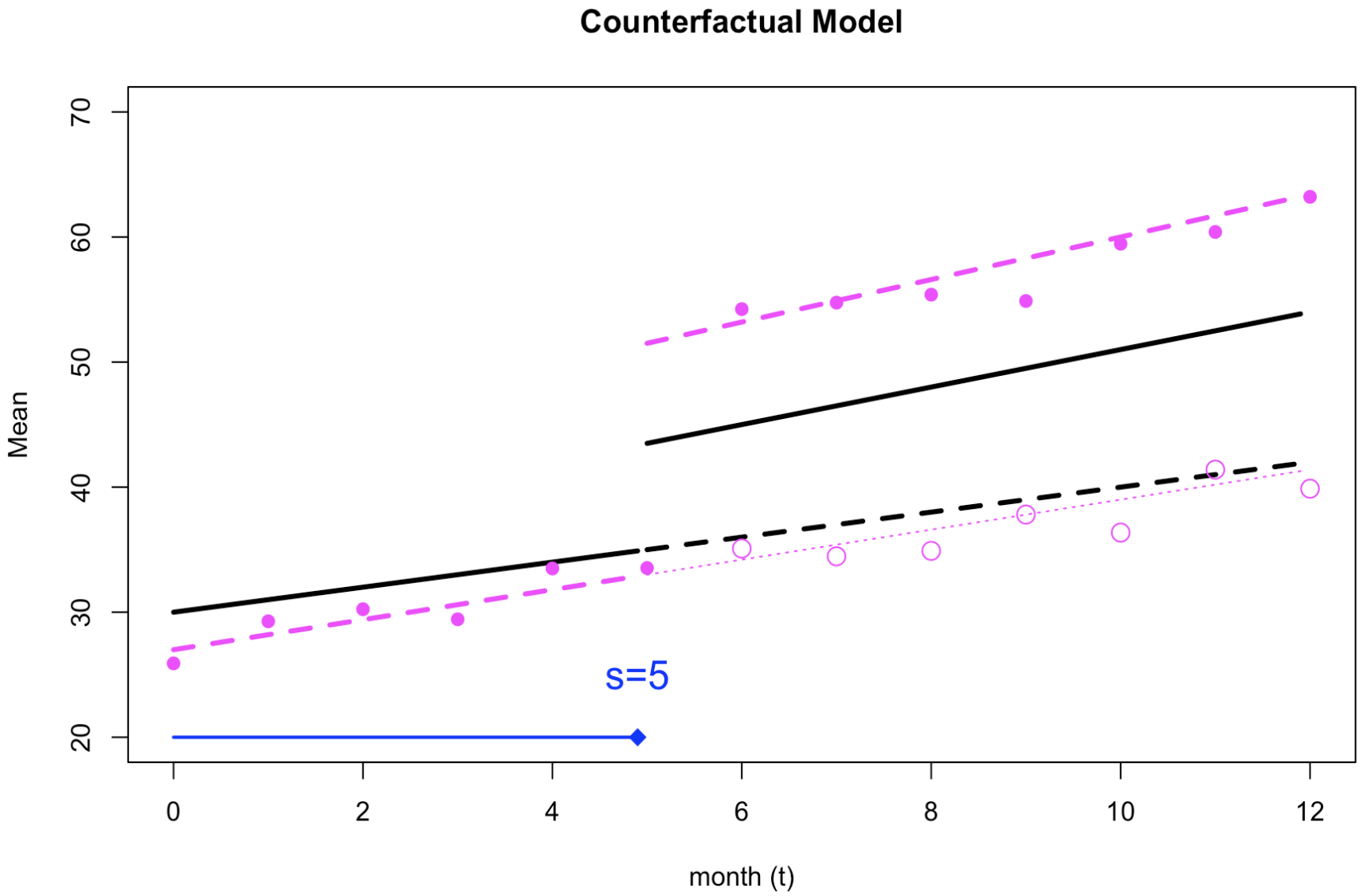
# Identifiability

- With **cross-sectional** data it is not possible to measure/approximate $\Delta_i$. The correlation between $Y_i(0)$ and $Y_i(1)$ is not identifiable.
- Goals:
  - With **longitudinal** data it is possible to narrow the non-identifiability, and to estimate p-ROC curves. (original goal of Sitlani and Heagerty, 2014)
  - **New**: or one can alter the classification goal to correctly discriminate between those that are expected to benefit from those who are not.

# Markers for Treatment Selection

- Crossover Trial

| subject | time 1 | time 2 | $\Delta$ |
|---|---|---|---|
| 101 | $Y_{i1}(1)$ | $Y_{i2}(0)$ | $\widehat{\Delta_i} = Y_{i1}(1) - Y_{i2}(0)$ |
| 102 | $Y_{i1}(0)$ | $Y_{i2}(1)$ | $\widehat{\Delta_i} = Y_{i2}(1) - Y_{i1}(0)$ |


Counterfactual Model
Mean
70
60
50
40
30
20
0
2
4
6
8
10
12
month (t)
s=5

# Longitudinal Structural Mixed Model

- Sitlani, Heagerty, Blood, and Tosteson (2012)
- Data: $X_i$=Tx assigned; $S_i$ = surgical time;
  Outcomes = $Y_i(S_i, t)$
- **Q**: How to model surgical outcome data with a given causal structure and (endogenous) surgical timing?

$$
\begin{aligned}
Y_i(s,t) \quad &= \quad \beta(t) \; + \; \gamma(s,t) \cdot 1(t > s) && \text{population} \\
&+ \; b_i(s,t) && \text{subject} \\
&+ \; e_i(s,t) && \text{observation}
\end{aligned}
$$

# Longitudinal Structural Mixed Model

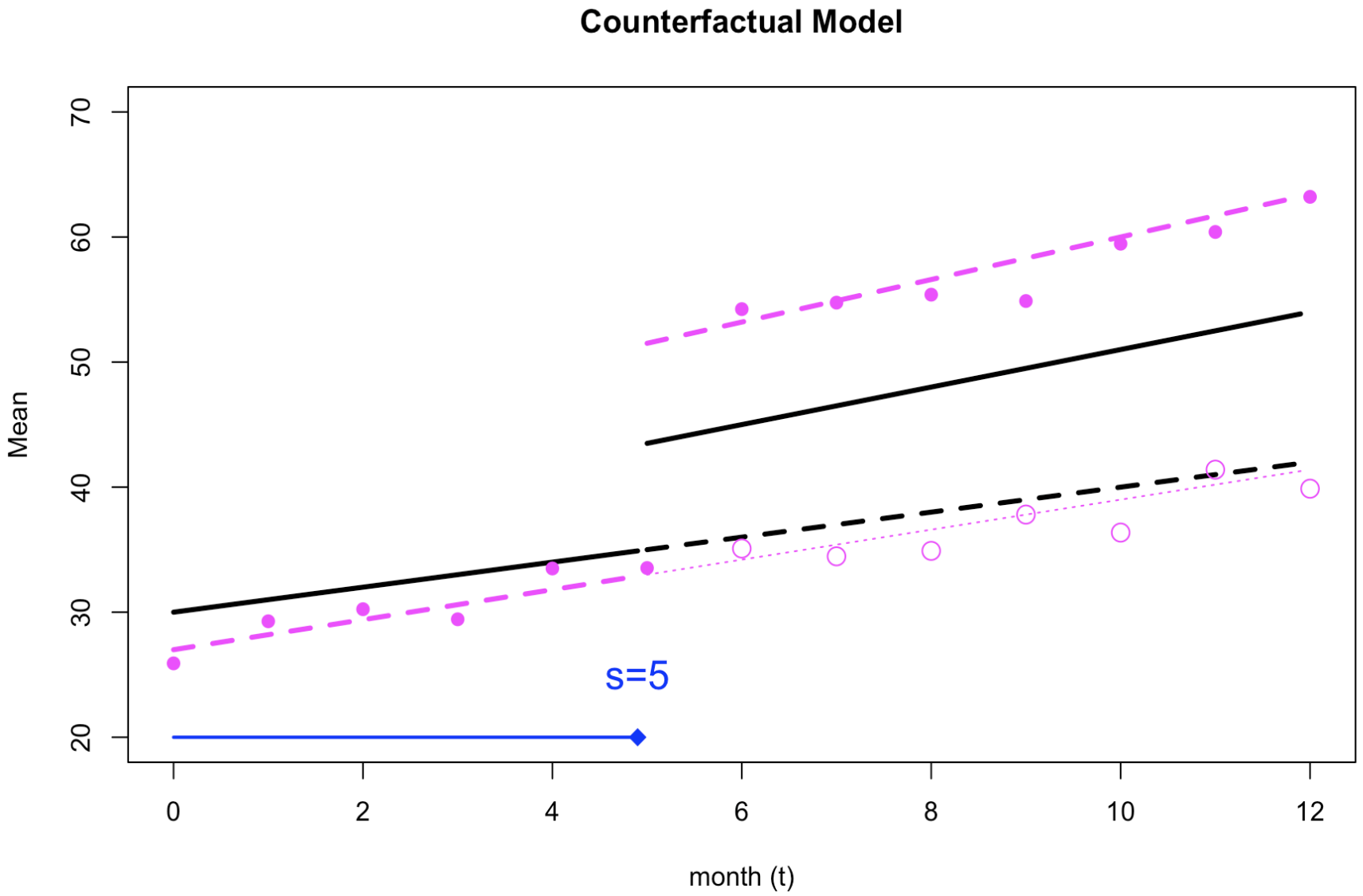
- Simple Example:

$$Y_i(s,t) = \beta_0 + \beta_1 \cdot t + [\gamma_0 + \gamma_1 \cdot (t-s)] \cdot 1(t > s)$$

$$+ b_{i,0} + b_{i,1} \cdot t + b_{i,2} \cdot 1(t > s)$$

$$+ e_{i,0}(t) \cdot 1(t \leq s) + e_{i,1}(t) \cdot 1(t > s)$$

distribution $b_i \sim \mathcal{N}, \; e_i \sim \mathcal{N}$


Counterfactual Model
Mean
20
30
40
50
60
70
0
2
4
6
8
10
12
month (t)
s=5

# Markers for Treatment Selection

- With a marker, $M_i$, we can define:

$$\Delta_i(s,t) \quad = \quad Y_i(s,t) - Y_i(t+,t)$$

potential outcomes at time $t$

surgery at time $s$ vs. no surgery through $t$

- We can extend the LSMM to include a marker:

$$\begin{aligned} Y_i(s,t) \quad &= \quad \beta(t,M_i) + \gamma(s,t,M_i) \cdot 1(t > s) \\ &\quad + b_i(s,t) + e_i(s,t) \end{aligned}$$

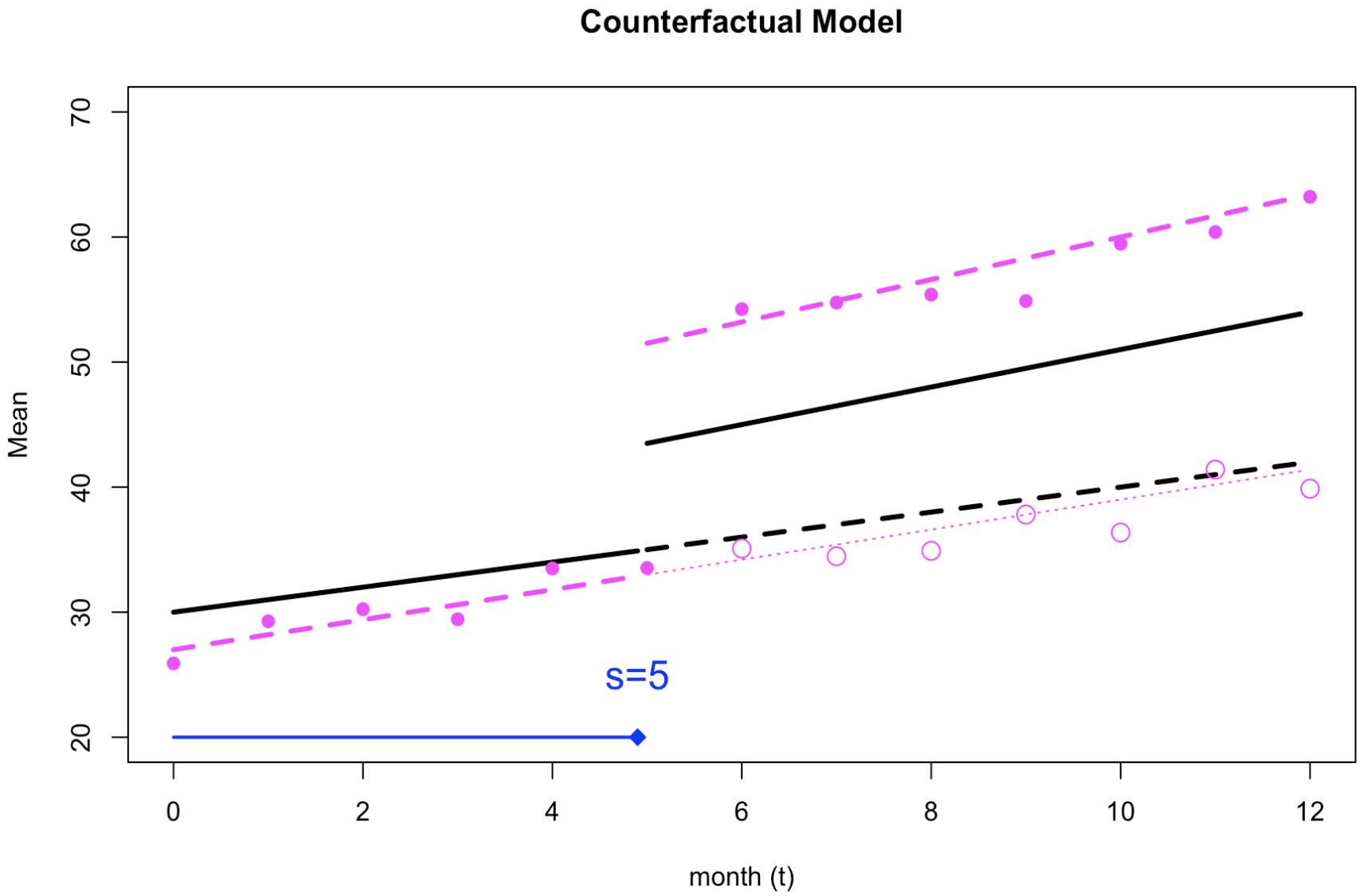
# Markers for Treatment Selection

- Using the LSMM allows us to write:

$$\begin{aligned} Y_i(s,t) - Y_i(t+,t) &= \gamma(s,t,M_i) \\ &\quad + [b_i(s,t) - b_i(t+,t)] \\ &\quad + [e_i(s,t) - e_i(t+,t)] \end{aligned}$$

- (Relatively) Simple example:

$$\begin{aligned} Y_i(s,t) &= \beta_0 + \beta_1 \cdot M_i + \beta_2 \cdot t + \beta_3 \cdot M_i \cdot t \\ &\quad + [\gamma_0 + \gamma_1 \cdot M_i + \gamma_2 \cdot (t-s)] \times 1(t > s) \\ &\quad + b_{i0} + b_{i1} \cdot t + b_{i2} \cdot 1(t > s) \\ &\quad + e_i(s,t) \end{aligned}$$


Counterfactual Model
Mean
70
60
50
40
30
20
0
2
4
6
8
10
12
month (t)
s=5

# Markers for Treatment Selection

- Using this "simple" example we see that for $t > s$:

$$\begin{aligned}\Delta_i(s,t) &= [\gamma_0 + \gamma_1 \cdot M_i + \gamma_2 \cdot (t-s)] \\ &\quad + b_{i2} \\ &\quad + [e_i(s,t) - e_i(t+,t)]\end{aligned}$$

- Define:

$$\begin{aligned}\text{p-Sensitivity} &: P[M_i > c \mid \Delta_i(s,t) > 0] \\ \text{p-Specificity} &: P[M_i \leq c \mid \Delta_i(s,t) \leq 0]\end{aligned}$$

# Markers for Treatment Selection

- Sitlani and Heagerty (2014) use:
  - ▷ LSMM for $[Y_i \mid M_i]$, and for $[M_i]$
  - ▷ Estimation for **p-Sens**, p-Spec, and ROC follows.

$$\begin{aligned} \text{p-Sens} &= P[M > c \mid \Delta > 0] \\ &= \frac{\int_c^\infty P[\Delta > 0 \mid M = m]\, P[M = m]\, dm}{\int_{-\infty}^\infty P[\Delta > 0 \mid M = m]\, P[M = m]\, dm} \end{aligned}$$

- Assumptions for $e_i(s,t) = [e_{i0}(t), e_{i1}(t)]$:
  - ▷ Uncorrelated errors: $e_{i0}(t) \perp e_{i1}(t)$
  - ▷ Equal errors: $e_{i0}(t) = e_{i1}(t)$

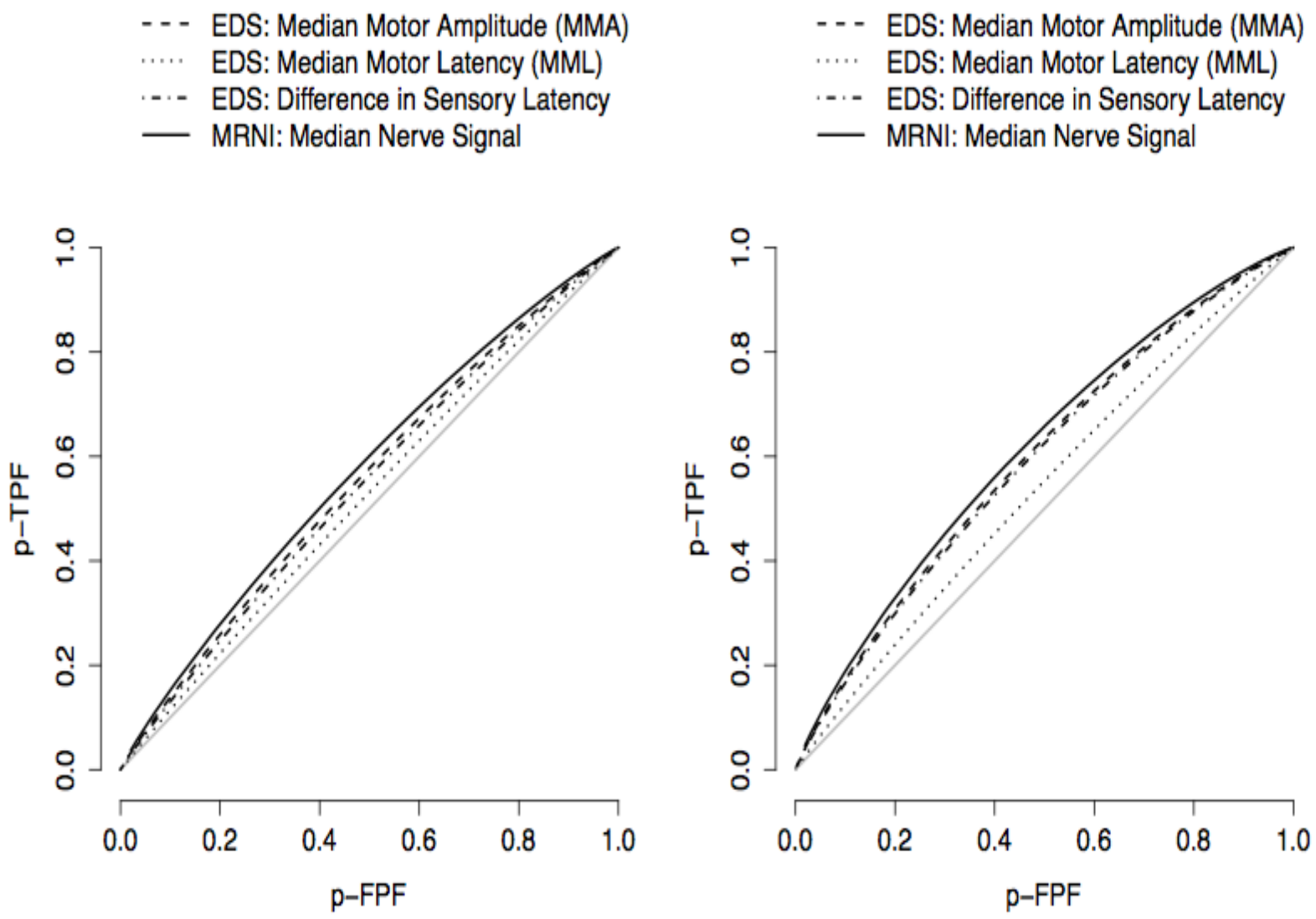



Fig. 4: p-ROC curve estimates for EDS and MRNI markers. The left panel assumes $e_i^0 \perp\!\!\!\perp e_i^1$, and the right panel assumes $e_i^0 = e_i^1$.

# Issue: non-identifiability

- Although $b_i$ is identifiable from longitudinal data, we still have unidentifiability of $e_i$.
- We have focused on:
  - ▷ Classification according to the **actual** (measured) difference between treated and untreated outcomes.
- Alternative:
  - ▷ Classification according to the **expected** difference between treated and untreated outcomes.

# Issue: non-identifiability

$$\begin{aligned}\Delta_i(s,t) &= [\gamma_0 + \gamma_1 \cdot M_i + \gamma_2 \cdot (t-s)] \\ &\quad + b_{i2} \\ &\quad + [e_i(s,t) - e_i(t+,t)]\end{aligned}$$

- Focus on the "expected benefit" of treatment:

$$\begin{aligned}\overline{\Delta}_i(s,t) = E_e[\Delta_i(s,t)] &= [\gamma_0 + \gamma_1 \cdot M_i + \gamma_2 \cdot (t-s)] \\ &\quad + b_{i2}\end{aligned}$$

- **Q**: what is this?

# Alternative

- Consider interest in benefit of treatment 2 years after surgery:

$$E_e[\Delta_i(2\text{yr})] = [\gamma_0 + \gamma_1 \cdot M_i + \gamma_2 \cdot (2)] + b_{i2}$$

- Expected magnitude of benefit averaging over **times** at which surgery could be initiated.
- Expected magnitude of benefit among **subpopulation** defined by $M_i$ and $b_{i2}$ – e.g. people similar to subject in both measured ($M_i$) and unmeasured subject-specific aspects ($b_{i2}$).

# Alternative

- Classification / discrimination according to expected benefit:
- Define:

$$\text{p-Sensitivity} \quad : \quad P[M_i > c \mid \overline{\Delta}_i(s,t) > 0]$$

$$\text{p-Specificity} \quad : \quad P[M_i \leq c \mid \overline{\Delta}_i(s,t) \leq 0]$$

- Shifts the classification goal to the **subject** level rather than focusing on the **observation** level.

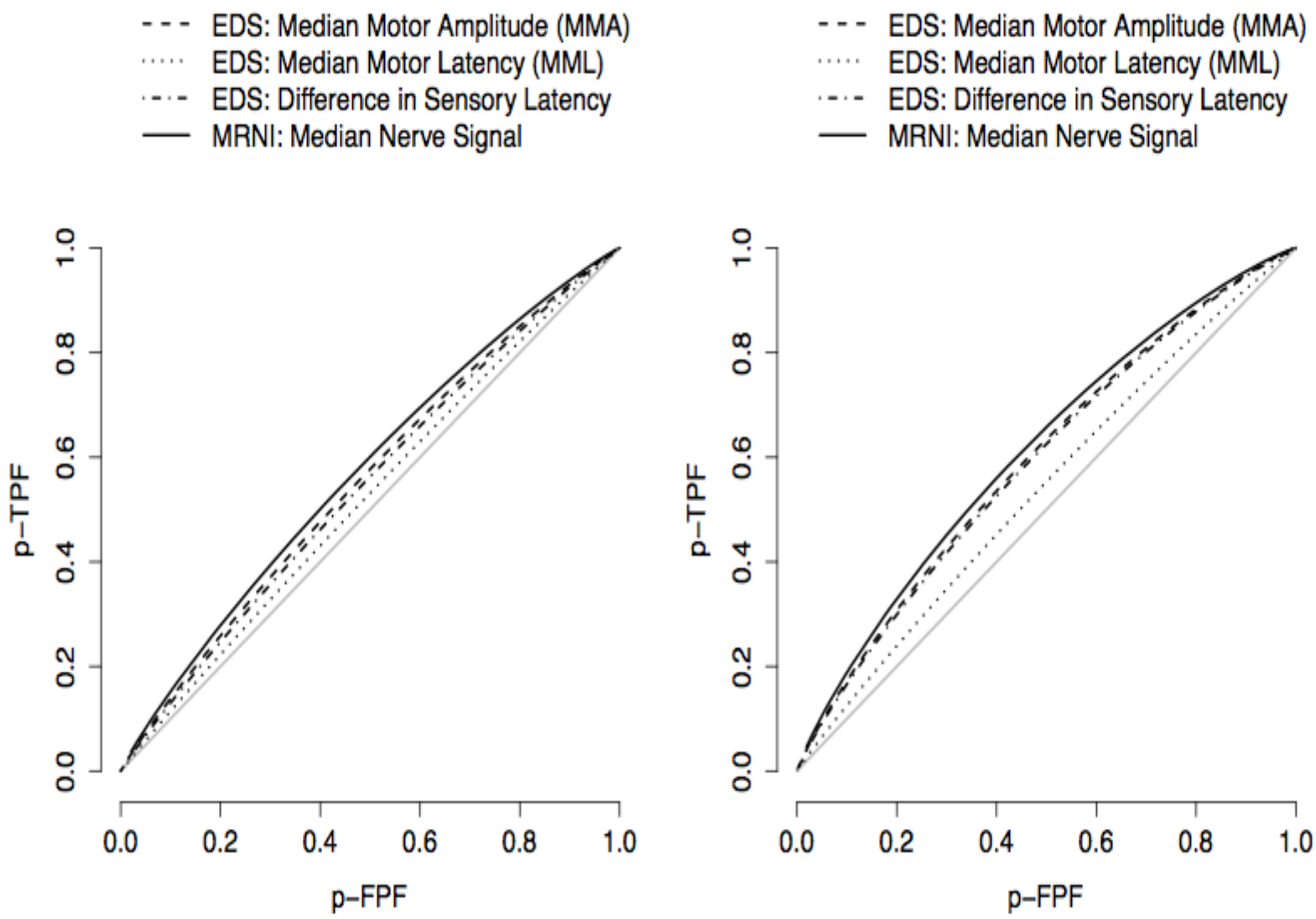



Fig. 4: p-ROC curve estimates for EDS and MRNI markers. The left panel assumes $e_i^0 \perp\!\!\!\perp e_i^1$, and the right panel assumes $e_i^0 = e_i^1$.

# Alternative(s)

- Cross-sectional data is inadequate for marker evaluation of treatment benefit.
- Longitudinal data allow options based on:

$$\begin{aligned} \textit{subject} \quad & \widehat{\Delta_i} = Y_{it}(1) - Y_{is}(0) \\ \textit{observation} \quad & \Delta_i(s,t) = Y_i(s,t) - Y_i(t+,t) \\ \textit{subject} \quad & \overline{\Delta}_i(s,t) = E_e[Y_i(s,t) - Y_i(t+,t)] \end{aligned}$$

# Summary

- Sitlani and Heagerty (2014) – *Stat Med*
- Define classification goal for treatment selection
- Longitudinal data is key to identification
- Parametric marker model (can be relaxed)
- **Colleen Sitlani**
- P01 CA053996-34, U54 RR024379, R01 HL072996-06