PROGRESSIVE
MULTIPLE SCLEROSIS

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Types OF MS

• Relapsing Remitting MS (RRMS)
• Secondary Progressive MS (SPMS)
• Progressive-Relapsing MS (PRMS)
• Primary Progressive MS (PPMS)

• Type determined by history/disease pattern/spontaneous remissions
Types of MS--Modified

• Relapsing Form of MS (RFMS)*
• Primary Progressive MS (PPMS)*

• Relapsing-Onset MS (ROMS)~
• Primary-Progressive MS (PPMS)~

Types of MS--Modified

• SPMS and PPMS are often linked together as “PROGRESSIVE MS.”
• Can result in confusion when studying results of research on different types.
• Similar to the recent controversy in the field of mental health regarding the new DSM-5.
NIMH Director Thomas Insel wrote about the DSM-5:

• “The weakness is its lack of validity. Unlike our definitions of ischemic heart disease, lymphoma, or AIDS, the DSM diagnoses are based on a consensus about clusters of clinical symptoms, not any objective laboratory measure.”

• “Patients with mental disorders deserve better…diagnosis by incorporating genetics, imaging, cognitive science, and other levels of information to lay the foundation for a new classification system…based on biomarkers…based on the emerging research date, not on the current symptom-based categories.”

• NIMHDirector’s BlogPost April 29, 2013
“Progressive” MS

Where did the concept come from that PPMS is the same as the SPMS phase of ROMS—that PPMS and SPMS are really the same?

Christian Confavreux, M.D.
Figure 2. Kaplan–Meier Estimates of the Time from the Onset of Multiple Sclerosis to the Assignment of a Score of 4 on the Kurtzke Disability Status Scale (Panel A), the Time from the Assignment of a Score of 4 to a Score of 6 (Panel B), and the Time from the Assignment of a Score of 6 to a Score of 7 (Panel C) among 1844 Patients with Multiple Sclerosis, According to the Initial Course.

Clinical differences between PPMS and ROMS

- **PPMS**
  - Onset ~ age 40
  - F/M = 1/1
  - Progression; may have exacerbations but no remissions
  - More cord & less brain disease load

- **RFMS**
  - Onset late 20s
  - F/M = 4/1
  - Exacerbations and remissions
  - More brain and less spinal cord disease load
Laboratory ways in which PPMS differs from SPMS

1) SPMS has high levels of serum anti-GAGA4 IgM; PPMS is negative for this assay.
2) MS serum autoantibody patterns distinguish PPMS from SPMS.
3) PPMS differs clearly from SPMS in leucocyte surface expression and soluble serum levels of adhesion molecules.

PPMS differs from SPMS

4) CSF protein profiles show differentiate between PPMS and RRMS.

5) Macular volume on OCT is lower in PPMS than SPMS.

6) fMRI demonstrates greater signal change on tactile stimulation in PPMS than SPMS.

7) On neuropsychological testing PPMS demonstrates generalized deficits; SPMS demonstrates focal deficits.


NERVE + ADJUVANT

NORMAL GUINEA PIG -> PARALYSIS
CEREBRAL CORTEX: LOCALIZATION OF FUNCTION AND ASSOCIATION PATHWAYS
## SEP Results

### Secondary progressive MS

#### Secondary Progressive Cursor Table

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<tr>
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<th>R Tibial-Average</th>
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<tr>
<td>N33</td>
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<tr>
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<td>83.4 ms</td>
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<tr>
<td>N22</td>
<td>20.8 ms</td>
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<td>PF</td>
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<tr>
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<tr>
<td>N33-P37</td>
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<td>0.05 uV</td>
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## Primary Progressive Cursor Table

### LTibial - Average

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<td>PF</td>
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### RTibial - Average

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Primary progressive MS
SEP conduction by MS group

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<tr>
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<td>46</td>
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Somatosensory Evoked Potentials in RFMS vs. PPMS--Results

- 83 MS patients studied—ROMS=53, PPMS=30
- Median SEPs *did not* contribute to differentiation.
- Tibial central conduction (CC) (N33-N22 [T12/L1]) *did* differentiate; if no T12/L1 obtained, N33 used.
- Amplitudes in PPMS showed greater attenuation than in RFMS.
- Normal CC seen in almost all (97%) PPMS patients; slow CC seen in 2/3 (68%) RFMS.
- Fisher’s exact test: There is a significant relationship between type of MS (RF vs. PP) and CC or N33 (p<0.01).
SEP Summary

• SEPs in MS can be useful in more ways than just identifying a “second site of disease” in the CNS.
• They are complementary to imaging and offer a window into the disease neurophysiology.
• Long-tract SEPs can be used to determine degree of demyelination vs. axonal disease.
• They can be helpful in determining the sub-category (relapsing forms vs. primary progressive) MS.
Progressive MS Conclusion

- Clinical differences between SP and PPMS
- Immunologic differences
- Neuropsychological differences
- Neurophysiological differences
- Strong argument for identification of heterogeneity in MS, to aid both understanding of disease process as well as direction of treatment