Correlating cognitive status with electrophysiological brain networks: An exploratory study in patients with Multiple Sclerosis

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Outline

- Introduction
- Multiple Sclerosis
- Materials and methods
- Results
- Conclusions
Introduction
History

Anthony Barker 1985

(University of Sheffield)

Transcranial magnetic stimulation (TMS)

- TMS is a non-invasive method of brain stimulation that relies on electromagnetic induction using an insulated coil placed over the scalp.

- During a TMS procedure, a magnetic field generator, or "coil" is placed near the head of the patient.

- The coil produces small electrical currents in the region of the brain just under the coil via electromagnetic induction.
Transcranial magnetic stimulation

LOCALIZED BRAIN-CELL EXCITATION results from the use of a transcranial magnetic stimulation (TMS) machine. When researchers operate a TMS coil near a subject’s scalp, a powerful and rapidly changing magnetic field passes safely and painlessly through skin and bone. Each brief pulse, lasting only microseconds, contains little energy. Because the strength of the magnetic field falls off rapidly with distance, it can penetrate only a few centimeters to the outer cortex of the brain (top right). On arrival, the precisely located field induces electric current in nearby neurons, thus activating targeted regions of the brain (bottom right). A principle benefit of TMS is that it requires no direct electrical connection to the body, as is required for electroconvulsive therapy.
Macroscopic response
- evoked neuronal activity (EEG)
- changes in blood flow and metabolism (PET, fMRI, NIRS, SPECT)
- muscle twitches (EMG)
- changes in behaviour

Microscopic response
- local depolarisation
- Axon membrane

Gershon et al., 2003
Physics

Biot-Savart Law

\[ d\mathbf{B} = \frac{\mu_0 I d\mathbf{L} \times \mathbf{l}_r}{4\pi r^2} \]

- Magnetic field of a current element
- \( d\mathbf{L} \): infinitesimal length of conductor carrying electric current \( I \)
- \( \mathbf{l}_r \): unit vector to specify the direction of the the vector distance \( r \) from the current to the field point.

Maxwell-Faraday equation

\[ \nabla \times \mathbf{E} = -\frac{d\mathbf{B}}{dt} \]
TMS in depression

Magnetic pulse to ease depression
A non-invasive procedure to help fight depression called transcranial magnetic stimulation, or TMS, uses a magnetic pulse to stimulate brain cells that control mood.

TMS treatment device

Limbic system structures
Thought to control emotional and behavioral patterns.

Short pulses of magnetic energy are focused at the limbic system structures.

Neuron
The pulses trigger electrical charges, causing neurons to become active.

SOURCE: Neuronetics

FDA approved 9 January 2013
TMS in migraine

• Approved for migraine with aura

• FDA approved 16 December 2013
Migraine treatment
Multiple sclerosis
MS symptoms

- Numbness, tingling: 63.5%
- Cognitive dysfunction: 13.4%
- Depression: 14.7%
- Fatigue: 40.1%
- Muscle spasms: 17.2%
- Weakness: 25.3%
- Walking difficulty: 48.9%
- Dizziness: 23.2%
- Vision problems: 40.2%
- Pain: 19.3%
- Bladder dysfunction: 11.1%
- Bowel dysfunction: 5.7%
Cognitive impairment

- 66% of respondents identified cognitive dysfunction as an MS symptom
- MS in America study (2,562 patients)
Cognitive Functions Affected in MS

- Memory - acquisition and retrieval
- Attention & concentration - working memory
- Speed of information processing
- Executive Functioning
- Visual/spatial organization
- Verbal fluency - word finding

The Impact of Cognitive Dysfunction In Daily Functioning

<table>
<thead>
<tr>
<th></th>
<th>Mean scale score</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Work status</td>
<td></td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Social activity</td>
<td></td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Personal assistance</td>
<td></td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Community services</td>
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<td>Financial status</td>
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<tr>
<td>Transportation</td>
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</tr>
<tr>
<td>Personal residence</td>
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</tbody>
</table>

Brain connectivity

Brain disconnection plays a major role in cognitive disabilities in MS. Leocani et al., 2000 investigated EEG coherence, which is the most widely used measure of interaction between brain areas, in patients with clinically definite MS and reported decreased coherence values in discrete bands compared to healthy subjects.
Materials and Methods
Subjects

10 patients with clinically definite MS according to the Poser’s criteria (8 women, median age 32 years, range 22-53)

11 age matched healthy controls (6 women, median age 26 years, range 19-47).
Exclusion criteria

- Severe cognitive decline
- Use of centrally active drugs (save for immunomodulatory treatments),
- contra-indications to Transcranial Magnetic Stimulation (TMS) and inability to understand and sign the informed consent or comply with the experimental procedures.
**Methods**

EEG recordings combined with TMS (TMS-EEG) were performed according to recent methodological guidelines (Ilmoniemi et al, 2010) in an electrically shielded room.

EEG was recorded with a 64-channel high density, TMS-compatible EEG device (eXimia, Nexstim Ltd., Helsinki, Finland).
Methods-2

For each patient, a 5 minute continuous resting state EEG was recorded with eyes opened every 30 sec followed by 5 minutes resting state EEG with eyes closed and TMS stimuli delivered every 15 seconds.

For the present analysis, we extracted the EEG segment of approximately 1.4 s prior to the time of TMS administration, containing 283 data points.
All subjects completed the experimental sessions and did not report any untoward side effects. We calculated the estimated values of imaginary coherence in patients and controls for five frequency bands:

- delta (δ)
- theta (Θ)
- alpha (α)
- beta (β)
- gamma (γ)

in relation to the three employed reference schemes:

- Mastoid
- Common Average
- REST
Brain waves examined

- **BETA**
  - 14 - 30 Hz
  - Awake, normal alert consciousness

- **ALPHA**
  - 9 - 13 Hz
  - Physically and mentally relaxed, awake but drowsy

- **DELTA**
  - Below 4 Hz
  - Deep (dreamless) sleep, loss of bodily awareness

- **THETA**
  - 4 - 8 Hz
  - Reduced consciousness, deep meditation, dreams, light sleep, REM sleep

- **GAMMA**
  - 30 Hz and above
  - Heightened perception
Results
In both patients and healthy controls, the Mastoid reference resulted in significantly lower icoh values compared to Common Average and REST (p<0.001) whereas the latter two references were not significantly different (p>0.05). This finding was consistent across all frequency bands (Fig 1). It should be noted that icoh values differed significantly in a frequency-specific manner (p<0.001).
Table 1. Imaginary coherence values in MS patients and healthy controls

<table>
<thead>
<tr>
<th>Group</th>
<th>icoh</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy subjects</td>
<td>0.11245</td>
<td>0.00103</td>
</tr>
<tr>
<td>MS patients</td>
<td>0.11425</td>
<td>0.001580</td>
</tr>
</tbody>
</table>
Table 2. Imaginary coherence values in MS patients and healthy controls (for the five frequency bands)

<table>
<thead>
<tr>
<th>Bands</th>
<th>icoth</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta</td>
<td>0.08680</td>
<td>0.00130</td>
</tr>
<tr>
<td>Theta</td>
<td>0.14524</td>
<td>0.00206</td>
</tr>
<tr>
<td>Alpha</td>
<td>0.16034</td>
<td>0.00188</td>
</tr>
<tr>
<td>Beta</td>
<td>0.10228</td>
<td>0.00153</td>
</tr>
<tr>
<td>Gamma</td>
<td>0.00702</td>
<td>0.00083</td>
</tr>
</tbody>
</table>
Table 3. Imaginary coherence values in MS patients and healthy controls (for the three reference schemes)

<table>
<thead>
<tr>
<th>Reference</th>
<th>$i_{coh}$</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastoid</td>
<td>0.0061</td>
<td>0.0009</td>
</tr>
<tr>
<td>Common Average</td>
<td>0.14001</td>
<td>0.00128</td>
</tr>
<tr>
<td>REST</td>
<td>0.13789</td>
<td>0.00133</td>
</tr>
</tbody>
</table>
Fig. 1  Icoh values for 5 frequency bands in relation to reference schemes
Neuropsychometric tests

MS patients scored below 2 S.D in working memory, verbal memory, information processing speed and attention indexes. Their overall cognitive functioning, as reflected by the total cognitive index, was also found to be impaired.

Scores in psychomotor functioning, executive functions and visual-spatial memory indexes were not found to exceed 2 S.D.
Table 4. Seven cognitive indexes and Total Cognitive Index scores are presented for MS patients and the healthy controls.

<table>
<thead>
<tr>
<th>Cognitive Index</th>
<th>Healthy Controls (n=9)</th>
<th>MS patients (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychomotor Functioning</td>
<td>-0.000(0.845)</td>
<td>0.629 (0.964)</td>
</tr>
<tr>
<td>Attention</td>
<td>-0.000(0.677)</td>
<td>-5.252(1.968)</td>
</tr>
<tr>
<td>Information Processing Speed</td>
<td>0.000(1.000)</td>
<td>-3.672(1.987)</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>0.000(0.974)</td>
<td>-2.937(1.283)</td>
</tr>
<tr>
<td>Working Memory</td>
<td>-0.000(0.910)</td>
<td>-2.430(1.279)</td>
</tr>
<tr>
<td>Executive Functions</td>
<td>0.000(.746)</td>
<td>-1.429(0.797)</td>
</tr>
<tr>
<td>Visual-Spatial Memory</td>
<td>0.000(0.956)</td>
<td>-1.586(0.804)</td>
</tr>
<tr>
<td>Total Cognitive Index</td>
<td>0.000(0.394)</td>
<td>-2.382(0.618)</td>
</tr>
</tbody>
</table>
The experimental paradigm employed in the present study was passive. Task-related parameters, such as the difficulty of the task, are critical determinants of the sensitivity of cognitive electrophysiological studies.

An active paradigm (for instance, involving the activation of a Working Memory network during EEG acquisition) may enhance the sensitivity of the methods. These approaches are currently under study.
Conclusions

Methodological factors (i.e. the choice of an appropriate reference scheme, a robust connectivity measure and a proper experimental paradigm) are of crucial importance for the construction of EEG-based brain networks for the investigation and monitoring of cognitive status in MS patients.
Thank you very much for your attention